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QH 301.5677

M.C

From: Huynh, Phuong N.
Sent: Tuesday, February 27, 2001 2:03 PM
To: STIC-ILL
Subject: RE: 09/187,693

Please deliver the following references:

J Cell Biol 116(2): 321-30; 1992

International J. of Oncology 13(2): 335-42; Aug 1998

International J. of Oncology 10(2): 339-347

J. of cellular biochemistry 51(2): 236-48

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NEWS 6	Oct 27	Plasdoc Key Serials Dictionary and Echoing added to Derwent Subscriber Files WPIDS and WPIX
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=> s antibody

L1 2131067 ANTIBODY

=> s l1 and epidermal growth factor receptor

4 FILES SEARCHED...
L2 7067 L1 AND EPIDERMAL GROWTH FACTOR RECEPTOR

=> s l2 and EGFR

L3 2494 L2 AND EGFR

=> s l2 and EGFR

L4 2494 L2 AND EGFR

=> s l4 and tyrosine phosphorylation

L5 187 L4 AND TYROSINE PHOSPHORYLATION

=> s l5 and inhibit

L6 30 L5 AND INHIBIT

=> s l6 and internalization

L7 0 L6 AND INTERNALIZATION

=> s l6 and degradation

L8 1 L6 AND DEGRADATION

=> d l8 all

L8 ANSWER 1 OF 1 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 97:483900 SCISEARCH
GA The Genuine Article (R) Number: XF539

TI Protein kinase C **inhibits epidermal growth factor receptor** phosphorylation in enterocytes

AU Summers S T (Reprint); Bass B L
CS VET ADM MED CTR, DEPT SURG, BALTIMORE, MD 21201 (Reprint); UNIV MARYLAND, SCH MED, BALTIMORE, MD 21201
CYA USA

SO JOURNAL OF SURGICAL RESEARCH, (APR 1997) Vol. 69, No. 1, pp. 208-211. Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 0022-4804.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 20

AB Epidermal growth factor (EGF) is an important proliferative signal in the gastrointestinal tract. The EGF receptor (**EGFr**), which transduces the mitogenic stimulus to the cell, may be regulated by a number of factors including extracellular matrix, cell-cell contact, and other peptides, As protein kinase C (PK-C) has been shown to phosphorylate and down-regulate the **EGFr** in certain tumor cell lines, we propose that PK-C, an important regulatory enzyme, modulates the phosphorylation of the **EGFr** in the IEC 6 rat enterocyte cell line. IEC 6 cells were cultured in dishes with Dulbecco's modified Eagle's medium, (DMEM)/5% fetal bovine serum (FBS), which was changed to DMEM/1% FBS 24 in prior to all experiments, Cells (three dishes per group) were treated with the PK-C activating phorbol ester phorbol-12-myristate-13-acetate (PMA) (100 nM) or vehicle for 1 hr and challenged with EGF (50 ng/ml) or vehicle for 15 min. Cell lysates were then prepared **EGFr tyrosine phosphorylation** was determined by immunoprecipitating the **EGFr** and immunoblotting with an **antibody** against phosphotyrosine, **EGFr** apparent molecular weight was assessed in the same lysates by Western blot with an anti-**EGFr antibody**. Blots were analyzed by computer densitometry. Data are expressed as mean +/- SEM; n = 3 with P value determined by t test. Exposure of cells to PMA resulted in a decrease in the EGF-stimulated **EGFr** phosphotyrosine content from 96 +/- 5 U in control to 66 +/- 6 U in PMA ($P < 0.01$). The amount of receptor did not change, 43 +/- 3 U in control vs 44 t 3 U in PMA ($P = 0.44$). Further, exposure to PMA in the absence of EGF caused a gel shift of the **EGFr** band consistent with a nontyrosine phosphorylation of the protein. We demonstrate that activation of PKC results in a modification of the **EGFr** coincident with inhibition of EGF-stimulated receptor tyrosine kinase activity. These data support a role for PR-C in the regulation of EG;Fr function and hence modulation of mitogenic signals in enterocytes. (C) 1997 Academic Press.

CC SURGERY

STP KeyWords Plus (R): INTESTINAL EPITHELIAL-CELLS; RAT SMALL-INTESTINE; PROLIFERATION; **DEGRADATION**; EXPRESSION

RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
BALIGA B S	1989	19	1045	BIOCHEM INT
BERNARD J A	1995	108	564	GASTROENTEROLOGY

BJORGE J D	1987	262	6615	J BIOL CHEM
CARROLL K M	1988	254	G355	AM J PHYSIOL
COCHET C	1984	259	2553	J BIOL CHEM
CRAVEN P A	1994	39	481	DIGEST DIS SCI
FERNANDEZPOL J A	1987	47	4260	CANCER RES
GROBLEWSKI G E	1992	263	G742	AM J PHYSIOL
HOLLEY R W	1977	74	5046	P NATL ACAD SCI USA
KAHLRAINER P	1994	15	779	CARCINOGENESIS
KEGEL M	1982	113	125	J CELL PHYSL
KO T C	1993	114	147	SURGERY
MALARKEY K	1995	309	361	BIOCHEM J
POLK D B	1994	107	109	GASTROENTEROLOGY
QUARONI A	1979	80	248	J CELL BIOL
SAXON M L	1994	126	747	J CELL BIOL
SEEDORF K	1995	270	18953	J BIOL CHEM
STOSCHECK C M	1984	98	1048	J CELL BIOL
WOLPERT S I	1996	171	109	AM J SURG
WOLPERT S I	1996	63	345	J SURG RES

=> d his

(FILE 'HOME' ENTERED AT 11:33:30 ON 27 FEB 2001)

FILE 'MEDLINE, BIOSIS, SCISEARCH, EMBASE, CAPLUS' ENTERED AT 11:33:51 ON 27 FEB 2001

L1 2131067 S ANTIBODY
L2 7067 S L1 AND EPIDERMAL GROWTH FACTOR RECEPTOR
L3 2494 S L2 AND EGFR
L4 2494 S L2 AND EGFR
L5 187 S L4 AND TYROSINE PHOSPHORYLATION
L6 30 S L5 AND INHIBIT
L7 0 S L6 AND INTERNALIZATION
L8 1 S L6 AND DEGRADATION

=> s l5 and KD

L9 6 L5 AND KD

=> d l9 all 1-6

L9 ANSWER 1 OF 6 MEDLINE
AN 1999194218 MEDLINE
DN 99194218
TI Eradication of established tumors by a fully human monoclonal **antibody** to the **epidermal growth factor receptor** without concomitant chemotherapy.
AU Yang X D; Jia X C; Corvalan J R; Wang P; Davis C G; Jakobovits A
CS Abgenix, Inc., Fremont, California 94555, USA.. yang_xd@abgenix.com
SO CANCER RESEARCH, (1999 Mar 15) 59 (6) 1236-43.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199906

AB A fully human IgG2kappa monoclonal **antibody** (MAb), E7.6.3, specific to the human epidermal growth factor (EGF) receptor (**EGFr**) was generated from human **antibody**-producing XenoMouse strains engineered to be deficient in mouse **antibody** production and to contain the majority of the human **antibody** gene repertoire on megabase-sized fragments from the human heavy and kappa light chain loci. The E7.6.3 MAb exhibits high affinity (**KD** = 5 x 10(-11) M) to the receptor, blocks completely the binding of both EGF and transforming growth factor alpha (TGF-a) to various **EGFr**-expressing human carcinoma cell lines, and abolishes EGF-dependent cell activation, including **EGFr tyrosine phosphorylation**, increased extracellular acidification rate, and cell proliferation. The **antibody** (0.2 mg i.p. twice a week for 3 weeks) prevents completely the formation of human epidermoid carcinoma A431 xenografts in athymic mice. More importantly, the administration of E7.6.3 without concomitant chemotherapy results in complete eradication of established tumors as large as 1.2 cm3. Tumor eradication of A431 xenografts was achieved in nearly all of the mice treated with total E7.6.3 doses as low as 3 mg, administered over the course of 3 weeks, and a total dose of 0.6 mg led to tumor elimination in 65% of the mice. No tumor recurrence was observed for more than 8 months after the last **antibody** injection, which further indicated complete tumor cell elimination by the **antibody**. The potency of E7.6.3 in eradicating well-established tumors without concomitant chemotherapy indicates its potential as a monotherapeutic agent for the treatment of multiple **EGFr** -expressing human solid tumors, including those for which no effective chemotherapy is available. Being a fully human **antibody**, E7.6.3 is expected to exhibit minimal immunogenicity and a longer half-life as compared with mouse or mouse-derivatized MAbs, thus allowing repeated **antibody** administration, including in immunocompetent patients. These results suggest E7.6.3 as a good candidate for assessing the full therapeutic potential of anti-**EGFr antibody** in the therapy of multiple patient populations with **EGFr**-expressing solid tumors.

CT Check Tags: Animal; Human; Male
***Antibodies, Monoclonal: TU, therapeutic use**
Antibody Affinity
*IgG: TU, therapeutic use
Immunotherapy
Mice
Mice, Inbred BALB C
Mice, Nude
Neoplasm Transplantation
Neoplasms, Experimental: PA, pathology
Neoplasms, Experimental: PC, prevention & control
*Neoplasms, Experimental: TH, therapy
*Receptor, Epidermal Growth Factor: IM, immunology
Transplantation, Heterologous

CN EC 2.7.11.- (Receptor, Epidermal Growth Factor); 0 (**Antibodies**, Monoclonal); 0.(IgG)

L9 ANSWER 2 OF 6 MEDLINE
AN 95032035 MEDLINE
DN 95032035
TI Nuclear localization of p185neu tyrosine kinase and its association with transcriptional transactivation.
AU Xie Y; Hung M C
CS Department of Tumor Biology, University of Texas M. D. Anderson Cancer

Center, Houston 77030.
NC CA58880 (NCI)
CA60856 (NCI)
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1994 Sep 30) 203 (3)
1589-98.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199501
AB The rat neu protooncogene encodes a 185 **kD** transmembrane protein (p185neu), which is a member of the **epidermal growth factor receptor** (**EGFr**) family. In searching for the signaling transducer of p185neu by using a two-hybrid selection system, we found, surprisingly, that the cytoplasmic domain of p185neu, when fused to the DNA-binding domain of GAL4 (amino acids 1-147), functioned as a transcriptional activator. We subsequently observed nuclear localization of p185neu. Interestingly, nuclear p185neu has a much higher extent of **tyrosine phosphorylation** than its nonnuclear counterpart. Our results suggest that a transmembrane receptor tyrosine kinase may enter the nucleus and be involved in transcriptional activation. This novel finding unveils a clue in the understanding of the mechanism of receptor tyrosine kinase-mediated signal transduction.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Line
*Cell Nucleus: ME, metabolism
Fluorescent Antibody Technique
Fungal Proteins: BI, biosynthesis
Fungal Proteins: ME, metabolism
*Gene Expression Regulation
*Genes, erbB-2
Plasmids
Promoter Regions (Genetics)
Protein-Tyrosine Kinase: AN, analysis
Protein-Tyrosine Kinase: BI, biosynthesis
*Protein-Tyrosine Kinase: ME, metabolism
Rats
Receptor, erbB-2: AN, analysis
Receptor, erbB-2: BI, biosynthesis
*Receptor, erbB-2: ME, metabolism
Recombinant Fusion Proteins: AN, analysis
Recombinant Fusion Proteins: ME, metabolism
Saccharomyces cerevisiae: GE, genetics
Saccharomyces cerevisiae: ME, metabolism
Sequence Deletion
Signal Transduction
*Transcription, Genetic
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.11.- (Receptor, erbB-2); 0 (Fungal Proteins); 0 (GAL4 protein, Saccharomyces); 0 (Plasmids); 0 (Recombinant Fusion Proteins)
GEN neu

L9 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:173234 BIOSIS
DN PREV199900173234

TI Eradication of established tumors by a fully human monoclonal **antibody** to the **epidermal growth factor receptor** without concomitant chemotherapy.

AU Yang, Xiao-Dong (1); Jia, Xiao-Chi; Corvalan, Jose R. F.; Wang, Ping; Davis, C. Geoffrey; Jakobovits, Aya

CS (1) Abgenix, Inc., 7601 Dumbarton Circle, Fremont, CA, 94555 USA

SO Cancer Research, (March 15, 1999) Vol. 59, No. 6, pp. 1236-1243. ISSN: 0008-5472.

DT Article

LA English

AB A fully human IgG2kappa monoclonal **antibody** (MAb), E7.6.3, specific to the human epidermal growth factor (EGF) receptor (**EGFr**) was generated from human **antibody**-producing XenoMouse strains engineered to be deficient in mouse **antibody** production and to contain the majority of the human **antibody** gene repertoire on megabase-sized fragments from the human heavy and kappa light chain loci. The E7.6.3 MAb exhibits high affinity (**KD** = 5 X 10-11 M) to the receptor, blocks completely the binding of both EGF and transforming growth factor alpha (TGF-alpha) to various **EGFr**-expressing human carcinoma cell lines, and abolishes EGF-dependent cell activation, including **EGFr tyrosine phosphorylation**, increased extracellular acidification rate, and cell proliferation. The **antibody** (0.2 mg i.p. twice a week for 3 weeks) prevents completely the formation of human epidermoid carcinoma A431 xenografts in athymic mice. More importantly, the administration of E7.6.3 without concomitant chemotherapy results in complete eradication of established tumors as large as 1.2 cm3. Tumor eradication of A431 xenografts was achieved in nearly all of the mice treated with total E7.6.3 doses as low as 3 mg, administered over the course of 3 weeks, and a total dose of 0.6 mg led to tumor elimination in 65% of the mice. No tumor recurrence was observed for more than 8 months after the last **antibody** injection, which further indicated complete tumor cell elimination by the **antibody**. The potency of E7.6.3 in eradicating well-established tumors without concomitant chemotherapy indicates its potential as a monotherapeutic agent for the treatment of multiple **EGFr**-expressing human solid tumors, including those for which no effective chemotherapy is available. Being a fully human **antibody**, E7.6.3 is expected to exhibit minimal immunogenicity and a longer half-life as compared with mouse or mouse-derivatized MAbs, thus allowing repeated **antibody** administration, including in immunocompetent patients. These results suggest E7.6.3 as a good candidate for assessing the full therapeutic potential of anti-**EGFr antibody** in the therapy of multiple patient populations with **EGFr**-expressing solid tumors.

CC Biochemical Studies - General *10060
Pharmacology - General *22002
Neoplasms and Neoplastic Agents - General *24002

BC Muridae 86375

IT Major Concepts
Biochemistry and Molecular Biophysics; Tumor Biology

IT Diseases
solid tumor: neoplastic disease

IT Chemicals & Biochemicals
human **epidermal growth factor receptor**; transforming growth factor-alpha; E7.6.3: IgG2 kappa monoclonal **antibody**

IT Alternate Indexing
Neoplasms (MeSH)

IT Methods & Equipment
chemotherapy: therapeutic method
IT Miscellaneous Descriptors
treatment development
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
XenoMouse (Muridae): animal model
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

L9 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 1999:193266 CAPLUS
DN 130:350943
TI Eradication of established tumors by a fully human monoclonal **antibody** to the **epidermal growth factor receptor** without concomitant chemotherapy
AU Yang, Xiao-Dong; Jia, Xiao-Chi; Corvalan, Jose R. F.; Wang, Ping; Davis, C. Geoffrey; Jakobovits, Aya
CS Abgenix, Inc., Fremont, CA, 94555, USA
SO Cancer Res. (1999), 59(6), 1236-1243
CODEN: CNREA8; ISSN: 0008-5472
PB AACR Subscription Office
DT Journal
LA English
CC 15-3 (Immunochemistry)
AB A fully human IgG2.kappa. monoclonal **antibody** (MAb), E7.6.3, specific to the human epidermal growth factor (EGF) receptor (**EGFr**) was generated from human **antibody**-producing XenoMouse strains engineered to be deficient in mouse **antibody** prodn. and to contain the majority of the human **antibody** gene repertoire on megabase-sized fragments from the human heavy and .kappa. light chain loci. The E7.6.3 MAb exhibits high affinity (**KD** = 5.times.10-11 M) to the receptor, blocks completely the binding of both EGF and transforming growth factor .alpha. (TGF-.alpha.) to various **EGFr**-expressing human carcinoma cell lines, and abolishes EGF-dependent cell activation, including **EGFr tyrosine phosphorylation**, increased extracellular acidification rate, and cell proliferation. The **antibody** (0.2 mg i.p. twice a week for 3 wk) prevents completely the formation of human epidermoid carcinoma A431 xenografts in athymic mice. More importantly, the administration of E7.6.3 without concomitant chemotherapy results in complete eradication of established tumors as large as 1.2 cm3. Tumor eradication of A431 xenografts was achieved in nearly all of the mice treated with total E7.6.3 doses as low as 3 mg, administered over the course of 3 wk, and a total dose of 0.6 mg led to tumor elimination in 65% of the mice. No tumor recurrence was obsd. for more than 8 mo after the last **antibody** injection, which further indicated complete tumor cell elimination by the **antibody**. The potency of E7.6.3 in eradicating well-established tumors without concomitant chemotherapy indicates its potential as a monotherapeutic agent for the treatment of multiple **EGFr**-expressing human solid tumors, including those for which no effective chemotherapy is available. Being a fully human **antibody**, E7.6.3 is expected to exhibit minimal immunogenicity and a longer half-life as compared with mouse or mouse-derivatized MAbs, thus

allowing repeated **antibody** administration, including in immunocompetent patients. These results suggest E7.6.3 as a good candidate for assessing the full therapeutic potential of anti-**EGFr antibody** in the therapy of multiple patient populations with **EGFr**-expressing solid tumors.

ST antitumor monoclonal **antibody** EGF receptor

IT Monoclonal immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(IgG2, E7.6.3; antitumor activity of human monoclonal **antibody** to EGF receptor)

IT **Epidermal growth factor receptors**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(antitumor activity of human monoclonal **antibody** to)

IT Receptor phosphorylation
(by EGF receptor is prevented by human monoclonal **antibody**)

IT Antitumor agents
(human monoclonal **antibody** to EGF receptor in relation to)

IT Transforming growth factor .alpha.
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(human monoclonal **antibody** to EGF receptor prevents binding by)

IT Breast carcinoma
(human monoclonal **antibody** to EGF receptor prevents proliferation of)

IT Cell proliferation
(human monoclonal **antibody** to EGF receptor prevents proliferation of breast carcinoma cells)

IT Cell activation
(human monoclonal **antibody** to EGF receptor prevents receptor-mediated activation of vulvar carcinoma cells)

IT IgG2
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(monoclonal, E7.6.3; antitumor activity of human monoclonal **antibody** to EGF receptor)

IT Female reproductive organ
(vulva, carcinoma; human monoclonal **antibody** to EGF receptor prevents receptor-mediated activation of)

IT Reproductive tract diseases
(vulvar carcinoma; human monoclonal **antibody** to EGF receptor prevents receptor-mediated activation of)

IT Carcinoma
(vulvar; human monoclonal **antibody** to EGF receptor prevents receptor-mediated activation of)

IT 79079-06-4, **Epidermal growth factor receptor** kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(antitumor activity of human monoclonal **antibody** to)

RE.CNT 33

RE

(1) Aboud-Pirak, E; J Natl Cancer Inst 1988, V80, P1605 CAPLUS
(2) Baselga, J; J Natl Cancer Inst 1993, V85, P1327 CAPLUS
(3) Baselga, J; Pharmacol Ther 1994, V64, P127 CAPLUS
(4) Bogovski, P; Tumours of Mouse 1994, P1 MEDLINE
(5) Cobleigh, M; Proc Am Soc Clin Oncol 1998, V17, P97
(6) Debanne, M; Baculovirus Expression Protocols 1995, P349 CAPLUS
(7) Ennis, B; Mol Endocrinol 1989, V3, P1830 CAPLUS

(8) Falcey, J; Proc Am Soc Clin Oncol 1997, V16, P383
(9) Fan, Z; Cancer Res 1993, V53, P4637 CAPLUS
(10) Fan, Z; Curr Opin Oncol 1998, V10, P67 CAPLUS
(11) Goldstein, N; Clin Cancer Res 1995, V1, P1311 CAPLUS
(12) Gullick, W; Br Med Bull 1991, V47, P87 CAPLUS
(13) Ishiyama, M; Biol Pharmacol Bull 1996, V19, P1518 CAPLUS
(14) Jakobovits, A; Exp Opin Invest Drugs 1998, V7, P607 CAPLUS
(15) Kawamoto, T; J Biol Chem 1984, V259, P7761 CAPLUS
(16) Kita, Y; Biochem Biophys Res Commun 1996, V226, P59 CAPLUS
(17) Masui, H; Cancer Res 1986, V46, P5592 CAPLUS
(18) McConnell, H; Science (Washington DC) 1992, V257, P1906 CAPLUS
(19) Mendelsohn, J; Biologic Therapy of Cancer 1995, P607
(20) Mendez, M; Nat Genet 1997, V15, P146 CAPLUS
(21) Modjtahedi, H; Br J Cancer 1993, V67, P247 CAPLUS
(22) Modjtahedi, H; Br J Cancer 1993, V67, P254 CAPLUS
(23) Modjtahedi, H; Cancer Res 1994, V54, P1695 CAPLUS
(24) Modjtahedi, H; Intl J Oncol 1994, V4, P277 CAPLUS
(25) Prewett, M; J Immunother Emphasis Tumor Immunol 1996, V19, P419 CAPLUS
(26) Riedel, H; Proc Natl Acad Sci USA 1988, V85, P1477 CAPLUS
(27) Salomon, D; Crit Rev Oncol Hematol 1995, V19, P183 MEDLINE
(28) Slamon, D; Proc Am Soc Clin Oncol 1998, V17, P98
(29) Slovin, S; Proc Am Soc Clin Oncol 1997, V16, P311
(30) Sturgis, E; Otolaryngol Head Neck Surg 1994, V111, P633 MEDLINE
(31) Ullrich, A; Cell 1990, V61, P203 CAPLUS
(32) Viloria Petit, A; Am J Pathol 1997, V151, P1523
(33) Wu, X; J Clin Invest 1995, V95, P1897 CAPLUS

L9 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 1996:71580 CAPLUS
DN 124:114575
TI Isolated polypeptide erbB-3, related to the **epidermal growth factor receptor** and **antibody** thereto
IN Kraus, Matthias H.; Aaronson, Stuart A.
PA United States Dept. of Health and Human Services, USA
SO U.S., 41 pp. Cont.-in-part of U.S. 5,183,884.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07K004-12
ICS C07K005-04; C07K014-71; C07K016-18
NCL 530326000
CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 15
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5480968	A	19960102	US 1992-978895	19921110
	US 444406	A0	19910315	US 1989-444406	19891201
	US 5183884	A	19930202		
	US 5820859	A	19981013	US 1995-473119	19950607
	US 5916755	A	19990629	US 1995-475352	19950607
PRAI	US 1989-444406	19891201			
	US 1992-978895	19921110			

AB A DNA fragment distinct from the **epidermal growth factor receptor** (**EGFR**) and erbB-2 genes was detected by reduced stringency hybridization of v-erbB to normal genomic human DNA. Characterization of the cloned DNA fragment mapped the region

of v-erbB homol. to three exons with closest homol. of 64% and 67% to a contiguous region within the tyrosine kinase domains of the **EGFR** and erbB-2 proteins, resp. cDNA cloning revealed a predicted 148 **kd** transmembrane polypeptide with structural features identifying it as a member of the erbB family, prompting designation of the new gene as erbB-3. It was mapped to human chromosome 12 q1 11-13 and was shown to be expressed as a 6.2 kb transcript in a variety of normal tissues of epithelial origin. Markedly elevated erbB-3 mRNA levels were demonstrated in certain human mammary tumor cell lines. These findings indicate that increased erbB-3 expression, as in the case of **EGFR** and erbB-2, plays a role in some human malignancies. Using erbB-3 specific **antibodies** (polyclonal or monoclonal), the erbB-3 protein was identified as a 180 kDa glycoprotein, gp180EGFR/erbB-3. The intrinsic catalytic function of gp180erbB-3 was uncovered by its ability to autophosphorylate in vitro. Ligand-dependent signaling of its cytoplasmic domain was established employing transfectants which express a chimeric **EGFR**/erbB-3 protein, gp180EGFR/erbB-3. EGF induced **tyrosine phosphorylation** of the chimera and promoted soft agar colony formation of such transfectants. These findings, combined with the detection of constitutive **tyrosine phosphorylation** of gp180erbB-3 in 4 out of 12 human mammary tumor cell lines, implicate the activated erbB-3 product in the pathogenesis of some human malignancies.

ST erbB3 gp180 malignancy

IT Cytotoxic agents
(conjugate with anti-gp180EGFR/erbB-3 **antibody**; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Peptides, biological studies
Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gp180EGFR/erbB-3-contg.; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Receptors
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(gp180EGFR/erbB-3; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Neoplasm
Neoplasm inhibitors
Protein sequences
(isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT **Antibodies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to gp180EGFR/erbB-3; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Gene, animal
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(c-erbB3, protein; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Deoxyribonucleic acid sequences
(complementary, isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Receptors
RL: PRP (Properties)
(gene c-erbB3, isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Glycoproteins, specific or class
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(gp180, gp180EGFR/erbB-3; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT 173147-30-3, Receptor (human clone pE3 gene c-erbB3)
RL: PRP (Properties)
(amino acid sequence; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT 147014-95-7, C-ErbB-3 protein kinase
RL: PRP (Properties)
(isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT 173147-29-0
RL: PRP (Properties)
(nucleotide sequence; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT 173073-14-8P 173073-15-9P 173073-16-0P 173073-17-1P 173073-18-2P
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polypeptide contg.; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

L9 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 1992:52332 CAPLUS
DN 116:52332
TI Association of the tyrosine phosphorylated **epidermal growth factor receptor** with a 55-**kD** tyrosine phosphorylated protein at the cell surface and in endosomes
AU Wada, Ikuo; Lai, Wei H.; Posner, Barry I.; Bergeron, John J. M.
CS Dep. Anat., McGill Univ., Montreal, PQ, H3A 2B2, Can.
SO J. Cell Biol. (1992), 116(2), 321-30
CODEN: JCLBA3; ISSN: 0021-9525
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB After the intraportal injection of EGF, the EGF receptor (**EGFR**) is rapidly internalized into hepatic endosomes where it remains largely receptor bound (Lai W. H., et al., 1989). In the present study, the phosphotyrosine content of **EGFRs** at the cell surface and in

endosomes was evaluated in order to assess the consequences of internalization. Quant. ests. of specific radioactivity of the **EGFR** in these 2 compartments revealed that **tyrosine phosphorylation** of the **EGFR** was obsd. at the cell surface within 30 s of ligand administration. However, the **EGFR** was also highly phosphorylated in endosomes reaching levels of **tyrosine phosphorylation** higher than those of the cell surface receptor at 5 and 15 min after EGF injection. A 55-kDa tyrosine phosphorylated polypeptide (pyp55) was obsd. in assocn. with the **EGFR** at the cell surface within 30 s of EGF injection. The protein was also found in assocn. with the **EGFR** in endosomes as evidenced by copptn. studies using a monoclonal **antibody** to the **EGFR** as well as by coelution with the EGR in gel permeation chromatog. Limited proteolysis of isolated endosomes indicated that the tyrosine phosphorylated domains of the **EGFR** and assocd. pyp55 were cytosolically oriented while internalized EGF was intraluminal. The identification of pyp55 in assocn. with **EGFR** in both hepatic plasma membranes and endosomes may be relevant to **EGFR** function and/or trafficking of the **EGFR**.

ST EGF receptor **tyrosine phosphorylation** internalization; endosome EGF receptor **tyrosine phosphorylation**; membrane EGF receptor **tyrosine phosphorylation**

IT Cell membrane
(EGF receptors of, phosphotyrosine of, of liver, endosome receptors in relation to)

IT Liver, composition
(EGF receptors of, **tyrosine phosphorylation** of, internalization in relation to)

IT Phosphorylation, biological
(of tyrosine, of EGF receptors in liver, internalization in relation to)

IT Organelle
(endocytic vesicle, EGF receptors of, phosphotyrosine of, of liver, cell membrane receptors in relation to)

IT Receptors
RL: BIOL (Biological study)
(epidermal growth factor, **tyrosine phosphorylation** of, of liver, internalization in relation to)

IT Biological transport
(internalization, of EGF receptors, in liver, **tyrosine phosphorylation** in relation to)

IT Phosphoproteins
RL: BIOL (Biological study)
(phosphotyrosine-contg., 55,000-mol.-wt., EGF receptor assocn. with, in cell membrane and endosome of hepatocyte, receptor **tyrosine phosphorylation** at internalization in relation to)

IT 62229-50-9D, EGF, receptor complexes
RL: PROC (Process)
(internalization of, in liver, **tyrosine phosphorylation** in relation to)

IT 60-18-4, Tyrosine, biological studies
RL: BIOL (Biological study)
(phosphorylation of, of EGF receptor in liver, internalization in relation to)

IT 62229-50-9, EGF
RL: BIOL (Biological study)
(receptors for, **tyrosine phosphorylation** of, in

liver, internalization in relation to)

```
=> d his

     (FILE 'HOME' ENTERED AT 11:33:30 ON 27 FEB 2001)

     FILE 'MEDLINE, BIOSIS, SCISEARCH, EMBASE, CAPLUS' ENTERED AT 11:33:51 ON
     27 FEB 2001
L1      2131067 S ANTIBODY
L2         7067 S L1 AND EPIDERMAL GROWTH FACTOR RECEPTOR
L3         2494 S L2 AND EGFR
L4         2494 S L2 AND EGFR
L5          187 S L4 AND TYROSINE PHOSPHORYLATION
L6           30 S L5 AND INHIBIT
L7            0 S L6 AND INTERNALIZATION
L8            1 S L6 AND DEGRADATION
L9            6 S L5 AND KD

=> s l5 and threonine phosphorylation

L10           0 L5 AND THREONINE PHOSPHORYLATION

=> s l4 and threonine phosphorylation

L11           0 L4 AND THREONINE PHOSPHORYLATION

=> dup remove l5

PROCESSING COMPLETED FOR L5
L12          73 DUP REMOVE L5 (114 DUPLICATES REMOVED)

=> s l12 and 63

L13           0 L12 AND 63

=> s l13 and 63 Kd

L14           0 L13 AND 63 KD

=> d l12 1-73


L12  ANSWER 1 OF 73  BIOSIS  COPYRIGHT 2001 BIOSIS      DUPLICATE 1
AN   2001:73051  BIOSIS
DN   PREV200100073051
TI   Epidermal growth factor receptor
     mediates stress-induced expression of its ligands in rat gastric
     epithelial cells.
AU   Miyazaki, Yoshiji (1); Hiraoka, Shintaro; Tsutsui, Syusaku; Kitamura,
     Shinji; Shinomura, Yasuhisa; Matsuzawa, Yuji
CS   (1) Department of Internal Medicine and Molecular Sciences, B5, Graduate
     School of Medicine, 2-2 Yamadaoka, Suita, Osaka, 565-0871:
     miyazaki@imed2.med.osaka-u.ac.jp Japan
SO   Gastroenterology, (January, 2001) Vol. 120, No. 1, pp. 108-116. print.
     ISSN: 0016-5085.
DT   Article
```

LA English
SL English

L12 ANSWER 2 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
AN 2001:70603 BIOSIS
DN PREV200100070603
TI Stimulation of the mitogen-activated protein kinase cascade and **tyrosine phosphorylation** of the **epidermal growth factor receptor** by hepatopoietin.
AU Li, Yong; Li, Ming; Xing, Guichun; Hu, Zhiyuan; Wang, Qingming; Dong, Chunna; Wei, Handong; Fan, Guocai; Chen, Jizhong; Yang, Xiaoming; Zhao, Shifu; Chen, Huipeng; Guan, Kunliang; Wu, Chutse; Zhang, Chenggang; He, Fuchu (1)
CS (1) Beijing Institute of Radiation Medicine, 27 Taiping Rd., Beijing, 100850: hefc@nic.bmi.ac.cn China
SO Journal of Biological Chemistry, (December 1, 2000) Vol. 275, No. 48, pp. 37443-37447. print.
ISSN: 0021-9258.
DT Article
LA English
SL English

L12 ANSWER 3 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:310879 SCISEARCH
GA The Genuine Article (R) Number: 304WU
TI Cross-talk between **epidermal growth factor receptor** and c-Met signal pathways in transformed cells
AU Jo M J; Stolz D B; Esplen J E; Dorko K; Michalopoulos G K; Strom S C (Reprint)
CS UNIV PITTSBURGH, SCH MED, DEPT PATHOL, 200 LOTHROP ST, BST S-450, PITTSBURGH, PA 15261 (Reprint); UNIV PITTSBURGH, SCH MED, DEPT PATHOL, PITTSBURGH, PA 15261; UNIV PITTSBURGH, SCH MED, DEPT PHYSIOL & CELL BIOL, PITTSBURGH, PA 15261
CYA USA
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (24 MAR 2000) Vol. 275, No. 12, pp. 8806-8811.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 42
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 4 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:528191 SCISEARCH
GA The Genuine Article (R) Number: 331XB
TI Integrin alpha 2 beta 1-dependent EGF receptor activation at cell-cell contact sites
AU Yu X; Miyamoto S; Mekada E (Reprint)
CS OSAKA UNIV, MICROBIAL DIS RES INST, DEPT CELL BIOL, 3-1 YAMADAOKA, SUITA, OSAKA 5650871, JAPAN (Reprint); KURUME UNIV, INST LIFE SCI, FUKUOKA 8390861, JAPAN; KURUME UNIV, RES CTR INNOVAT CANC THERAPY, FUKUOKA 8390861, JAPAN; KYUSHU NATL CANC CTR, GYNECOL SERV, MINAMI KU, FUKUOKA 8111395, JAPAN
CYA JAPAN
SO JOURNAL OF CELL SCIENCE, (JUN 2000) Vol. 113, No. 12, pp. 2139-2147.

Publisher: COMPANY OF BIOLOGISTS LTD, BIDDER BUILDING CAMBRIDGE COMMERCIAL
PARK COWLEY RD, CAMBRIDGE CB4 4DL, CAMBS, ENGLAND.
ISSN: 0021-9533.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 50
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 5 OF 73 MEDLINE DUPLICATE 3
AN 2000473231 MEDLINE
DN 20444296
TI Lysophosphatidic acid inhibits Ca2+ signaling in response to **epidermal growth factor receptor** stimulation in human astrocytoma cells by a mechanism involving phospholipase C(gamma) and a G(alphai) protein.
AU Hernandez M; Barrero M J; Crespo M S; Nieto M L
CS Instituto de Biologia y Genetica Molecular, CSIC-Universidad de Valladolid, Valladolid, Spain.
SO JOURNAL OF NEUROCHEMISTRY, (2000 Oct) 75 (4) 1575-82.
Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200012
EW 20001202

L12 ANSWER 6 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 4
AN 2000:939453 SCISEARCH
GA The Genuine Article (R) Number: 380WL
TI Cellular signaling by **tyrosine phosphorylation** in keloid and normal human dermal fibroblasts
AU Chin G S; Liu W; Steinbrech D; Hsu M; Levinson H; Longaker M T (Reprint)
CS STANFORD UNIV, SCH MED, DEPT SURG, H3680, 300 PASTEUR DR, STANFORD, CA 94305 (Reprint); NYU, MED CTR, DEPT SURG, LAB DEV BIOL & REPAIR, NEW YORK, NY 10016
CYA USA
SO PLASTIC AND RECONSTRUCTIVE SURGERY, (DEC 2000) Vol. 106, No. 7, pp. 1532-1540.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621.
ISSN: 0032-1052.
DT Article; Journal
FS LIFE; CLIN
LA English
REC Reference Count: 70
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 7 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001016690 EMBASE
TI Critical role of extracellular signal-regulated kinase (ERK) phosphorylation in novel vitamin K analog-induced cell death.
AU Osada S.; Carr B.I.
CS S. Osada, Department of Surgery, Thomas E. Starzl Transplant. Inst., University of Pittsburgh, Pittsburgh, PA 15213, United States.

CYPO5471@nifty.ne.jp
SO Japanese Journal of Cancer Research, (2000) 91/12 (1250-1257).
Refs: 32
ISSN: 0910-5050 CODEN: JJCREP
CY Japan
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English

L12 ANSWER 8 OF 73 MEDLINE DUPLICATE 5
AN 2000131152 MEDLINE
DN 20131152
TI Mechanical stretch stimulates growth of vascular smooth muscle cells via **epidermal growth factor receptor**.
AU Iwasaki H; Eguchi S; Ueno H; Marumo F; Hirata Y
CS Division of Endocrinology and Metabolism, Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo 113-8519, Japan.
SO Am J Physiol Heart Circ Physiol, (2000 Feb) 278 (2) H521-9.
Journal code: DKM. ISSN: 0363-6135.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
EW 20000501

L12 ANSWER 9 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 6
AN 2000:347836 BIOSIS
DN PREV200000347836
TI Tri-iodothyronine induces proliferation in cultured bovine thyroid cells: Evidence for the involvement of epidermal growth factor-associated tyrosine kinase activity.
AU Di Fulvio, M. (1); Coleoni, A. H.; Pellizas, C. G.; Masini-Repiso, A. M.
CS (1) Departamento de Bioquimica Clinica, Facultad de Ciencias Quimicas, Universidad Nacional de Cordoba, Ciudad Universitaria, 5000, Cordoba Argentina
SO Journal of Endocrinology, (July, 2000) Vol. 166, No. 1, pp. 173-182. print.
ISSN: 0022-0795.
DT Article
LA English
SL English

L12 ANSWER 10 OF 73 MEDLINE DUPLICATE 7
AN 2000078900 MEDLINE
DN 20078900
TI Ratiometric assay of **epidermal growth factor receptor** tyrosine kinase activation.
AU Schooler K; Wiley H S
CS Division of Cell Biology, University of Utah, Salt Lake City, Utah, 84132,
USA.
SO ANALYTICAL BIOCHEMISTRY, (2000 Jan 1) 277 (1) 135-42.

Journal code: 4NK. ISSN: 0003-2697.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200006
EW 20000604

L12 ANSWER 11 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 8
AN 2001:59031 BIOSIS
DN PREV200100059031
TI Enhanced apoptosis with combination C225/radiation treatment serves as the
impetus for clinical investigation in head and neck cancers.
AU Bonner, James A. (1); Raisch, Kevin P.; Trummell, Hoa Q.; Robert, Francisco; Meredith, Ruby F.; Spencer, Sharon A.; Buchsbaum, Donald J.; Saleh, Mansoor N.; Stackhouse, Murray A.; LoBuglio, Albert F.; Peters, Glenn E.; Carroll, William R.; Waksal, Harlan W.
CS (1) Department of Radiation Oncology, University of Alabama at Birmingham,
1530 3rd Ave South, WTI 105, Birmingham, AL, 35294-3300 USA
SO Journal of Clinical Oncology, (November 1, 2000) Vol. 18, No. 21 Supplement, pp. 47s-53s. print.
ISSN: 0732-183X.
DT Article
LA English
SL English

L12 ANSWER 12 OF 73 CAPLUS COPYRIGHT 2001 ACS
AN 2000:822458 CAPLUS
TI Enhanced apoptosis with combination C225/radiation treatment serves as the
impetus for clinical investigation in head and neck cancers
AU Bonner, James A.; Raisch, Kevin P.; Trummell, Hoa Q.; Robert, Francisco; Meredith, Ruby F.; Spencer, Sharon A.; Buchsbaum, Donald J.; Saleh, Mansoor N.; Stackhouse, Murray A.; LoBuglio, Albert F.; Peters, Glenn E.; Carroll, William R.; Waksal, Harlan W.
CS Comprehensive Cancer Center (Experimental Therapeutics Program), University of Alabama at Birmingham, Birmingham, AL, 35294-3300, USA
SO J. Clin. Oncol. (2000), 18(21, Suppl.), 47S-53S
CODEN: JCONDN; ISSN: 0732-183X
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 35
RE
(1) Bonner, J; Int J Radiat Oncol Biol Phys 1994, V29, P243 CAPLUS
(2) Bonner, J; Int J Radiat Oncol Biol Phys 1998, V42, P921 CAPLUS
(6) Contessa, J; Clin Cancer Res 1999, V5, P405 CAPLUS
(8) David, M; J Biol Chem 1996, V271, P9185 CAPLUS
(12) Grandis, J; J Clin Invest 1998, V102, P1385 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:12020 SCISEARCH
GA The Genuine Article (R) Number: 267WR
TI Activation of **epidermal growth factor receptor** promotes late terminal differentiation of cell-matrix

interaction-disrupted keratinocytes
AU Wakita N (Reprint); Takigawa M
CS HAMAMATSU UNIV, SCH MED, DEPT DERMATOL, 3600 HANDA CHO, HAMAMATSU, SHIZUOKA 431319, JAPAN (Reprint)
CYA JAPAN
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (24 DEC 1999) Vol. 274, No. 52, pp. 37285-37291.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 45
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 14 OF 73 MEDLINE DUPLICATE 9
AN 1999214601 MEDLINE
DN 99214601
TI Keratinocyte collagenase-1 expression requires an **epidermal growth factor receptor** autocrine mechanism.
AU Pilcher B K; Dumin J; Schwartz M J; Mast B A; Schultz G S; Parks W C; Welgus H G
CS Division of Dermatology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110, USA..
bpilcher@im.wustl.edu
NC K-01
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Apr 9) 274 (15) 10372-81.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199907

L12 ANSWER 15 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1999:581209 SCISEARCH
GA The Genuine Article (R) Number: 219PQ
TI **Epidermal growth factor receptor** internalization rate is regulated by negative charges near the SH2 binding site tyr992
AU Holbrook M R; ODonnell J B; Slakey L L; Gross D J (Reprint)
CS UNIV MASSACHUSETTS, DEPT BIOCHEM & MOL BIOL, PROGRAM MOL & CELLULAR BIOL, LEDERLE GRC, AMHERST, MA 01003 (Reprint); UNIV MASSACHUSETTS, DEPT BIOCHEM & MOL BIOL, PROGRAM MOL & CELLULAR BIOL, AMHERST, MA 01003; UNIV MASSACHUSETTS, COLL NAT SCI & MATH, AMHERST, MA 01003
CYA USA
SO BIOCHEMISTRY, (20 JUL 1999) Vol. 38, No. 29, pp. 9348-9356.
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
ISSN: 0006-2960.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 50
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 16 OF 73 MEDLINE DUPLICATE 10
AN 1999427869 MEDLINE
DN 99427869
TI Endothelin-mediated vascular growth requires p42/p44 mitogen-activated protein kinase and p70 S6 kinase cascades via transactivation of **epidermal growth factor receptor**.
AU Iwasaki H; Eguchi S; Ueno H; Marumo F; Hirata Y
CS Second Department of Internal Medicine, Tokyo Medical and Dental University, Japan.
SO ENDOCRINOLOGY, (1999 Oct) 140 (10) 4659-68.
Journal code: EGZ. ISSN: 0013-7227.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199912

L12 ANSWER 17 OF 73 MEDLINE DUPLICATE 11
AN 1999365145 MEDLINE
DN 99365145
TI Radiation-induced release of transforming growth factor alpha activates the **epidermal growth factor receptor** and mitogen-activated protein kinase pathway in carcinoma cells, leading to increased proliferation and protection from radiation-induced cell death.
AU Dent P; Reardon D B; Park J S; Bowers G; Logsdon C; Valerie K; Schmidt-Ullrich R
CS Department of Radiation Oncology, Massey Cancer Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298, USA.. PDENT@HSC.VCU.EDU
NC P01CA72955 (NCI)
R01CA65896 (NCI)
SO MOLECULAR BIOLOGY OF THE CELL, (1999 Aug) 10 (8) 2493-506.
Journal code: BAU. ISSN: 1059-1524.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199912

L12 ANSWER 18 OF 73 MEDLINE DUPLICATE 12
AN 1999310812 MEDLINE
DN 99310812
TI 4-hydroxynonenal triggers an **epidermal growth factor receptor**-linked signal pathway for growth inhibition.
AU Liu W; Akhand A A; Kato M; Yokoyama I; Miyata T; Kurokawa K; Uchida K; Nakashima I
CS Department of Immunology, Nagoya University School of Medicine, Showa-ku, Nagoya 466-8550, Japan.
SO JOURNAL OF CELL SCIENCE, (1999 Jul) 112 (Pt 14) 2409-17.
Journal code: HNK. ISSN: 0021-9533.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199912

L12 ANSWER 19 OF 73 MEDLINE DUPLICATE 13
AN 1999194218 MEDLINE
DN 99194218
TI Eradication of established tumors by a fully human monoclonal **antibody** to the **epidermal growth factor receptor** without concomitant chemotherapy.
AU Yang X D; Jia X C; Corvalan J R; Wang P; Davis C G; Jakobovits A
CS Abgenix, Inc., Fremont, California 94555, USA.. yang_xd@abgenix.com
SO CANCER RESEARCH, (1999 Mar 15) 59 (6) 1236-43.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199906

L12 ANSWER 20 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:2954 BIOSIS
DN PREV200000002954
TI Ionizing radiation stimulates existing signal transduction pathways involving the activation of **epidermal growth factor receptor** and erbB-3, and changes of intracellular calcium in A431 human squamous carcinoma cells.
AU Todd, D. G. (1); Mikkelsen, R. B. (1); Rorrer, W. K. (1); Valerie, K. (1);
Schmidt-Ullrich, R. K. (1)
CS (1) Department of Radiation Oncology, Medical College of Virginia/Virginia
Commonwealth University, Richmond, VA, 23298-0058 USA
SO Journal of Receptor and Signal Transduction Research, (Nov., 1999) Vol. 19, No. 6, pp. 885-908.
ISSN: 1079-9893.
DT Article
LA English
SL English

L12 ANSWER 21 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1999:803044 SCISEARCH
GA The Genuine Article (R) Number: 246DW
TI Inhibition of **epidermal growth factor receptor**-associated **tyrosine phosphorylation** in human carcinomas with CP-358,774: Dynamics of receptor inhibition in situ and antitumor effects in athymic mice
AU Pollack V A (Reprint); Savage D M; Baker D A; Tsaparikos K E; Sloan D E; Moyer J D; Barbacci E G; Pustilnik L R; Smolarek T A; Davis J A; Vaidya M P; Arnold L D; Doty J L; Iwata K K; Morin M J
CS PFIZER INC, CENT RES, DEPT GENOM TARGETS & CANC RES, EASTERN POINT RD, GROTON, CT 06340 (Reprint)
CYA USA
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (NOV 1999) Vol. 291, No. 2, pp. 739-748.
Publisher: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS, 9650 ROCKVILLE
PIKE, BETHESDA, MD 20814-3998.
ISSN: 0022-3565.
DT Article; Journal
FS LIFE

LA English
REC Reference Count: 52
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 22 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:112903 BIOSIS
DN PREV199900112903
TI 1,25-Dihydroxyvitamin D3 increases the growth-promoting activity of autocrine **epidermal growth factor receptor** ligands in keratinocytes.
AU Garach-Jehoshua, Osnat; Ravid, Amiram; Liberman, Uri A.; Koren, Ruth (1)
CS (1) Felsenstein Med. Res. Cent., Rabin Med. Cent., Beilinson Campus, Petah Tikva 49100 Israel
SO Endocrinology, (Feb., 1999) Vol. 140, No. 2, pp. 713-721.
ISSN: 0013-7227.
DT Article
LA English

L12 ANSWER 23 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1999:192347 SCISEARCH
GA The Genuine Article (R) Number: 172CU
TI Transforming growth factor-alpha short-circuits downregulation of the **epidermal growth factor receptor**
AU Ouyang X M; Gulliford T; Huang G C; Epstein R J (Reprint)
CS HAMMERSMITH HOSP, IMPERIAL COLL SCH MED, DEPT METAB MED, ROOM 5S1, COMMONWEALTH BLDG, DU CANE RD, LONDON W12 0NN, ENGLAND (Reprint); IMPERIAL COLL SCH MED, DEPT METAB MED, LONDON, ENGLAND; IMPERIAL COLL SCH MED, DEPT ONCOL, LONDON, ENGLAND
CYA ENGLAND
SO JOURNAL OF CELLULAR PHYSIOLOGY, (APR 1999) Vol. 179, No. 1, pp. 52-57.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.
ISSN: 0021-9541.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 35
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 24 OF 73 MEDLINE DUPLICATE 14
AN 2000029737 MEDLINE
DN 20029737
TI In vitro endosome-lysosome transfer of dephosphorylated EGF receptor and Shc in rat liver.
AU Authier F; Chauvet G
CS Institut National de la Sante et de la Recherche Medicale U510, Faculte de Pharmacie Paris XI, 5 rue Jean-Baptiste Clement, 92296, Chatenay-Malabry, France.. francois.authier@cep.u-psud.fr
SO FEBS LETTERS, (1999 Nov 12) 461 (1-2) 25-31.
Journal code: EUH. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals; Cancer Journals
EM 200002
EW 20000204

L12 ANSWER 25 OF 73 MEDLINE DUPLICATE 15
AN 1999041949 MEDLINE
DN 99041949
TI Peroxynitrite induces covalent dimerization of **epidermal growth factor receptors** in A431 epidermoid carcinoma cells.
AU van der Vliet A; Hristova M; Cross C E; Eiserich J P; Goldkorn T
CS Center for Comparative Respiratory Biology and Medicine, Department of Internal Medicine, University of California, Davis, California 95616, USA.
NC HL57452 (NHLBI)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Nov 27) 273 (48) 31860-6. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199902

L12 ANSWER 26 OF 73 MEDLINE DUPLICATE 16
AN 1998362025 MEDLINE
DN 98362025
TI EAST, an **epidermal growth factor receptor**- and Eps15-associated protein with Src homology 3 and tyrosine-based activation motif domains.
AU Lohi O; Poussu A; Merilainen J; Kellokumpu S; Wasenius V M; Lehto V P
CS Department of Pathology, University of Oulu, Oulu, FIN-90220, Finland.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Aug 14) 273 (33) 21408-15. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-AJ224514
EM 199811

L12 ANSWER 27 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1998:948401 SCISEARCH
GA The Genuine Article (R) Number: 146NJ
TI Reciprocal interactions between beta 1-integrin and **epidermal growth factor receptor** in three-dimensional basement membrane breast cultures: A different perspective in epithelial biology
AU Wang F; Weaver V M; Petersen O W; Larabell C A; Dedhar S; Briand P; Lupu R; Bissell M J (Reprint)
CS UNIV CALIF BERKELEY, LAWRENCE BERKELEY LAB, DIV LIFE SCI, BERKELEY, CA 94720 (Reprint); UNIV CALIF BERKELEY, LAWRENCE BERKELEY LAB, DIV LIFE SCI, BERKELEY, CA 94720; UNIV COPENHAGEN, PANUM INST, INST MED ANAT, STRUCT CELL BIOL UNIT, DK-2200 COPENHAGEN N, DENMARK; JACK BELL RES CTR, VANCOUVER, BC V6H 3Z6, CANADA; DANISH CANC SOC, DIV CANC BIOL, DEPT TUMOR ENDOCRINOL, DK-2100 COPENHAGEN O, DENMARK
CYA USA; DENMARK; CANADA
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF

AMERICA, (8 DEC 1998) Vol. 95, No. 25, pp. 14821-14826.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418.
ISSN: 0027-8424.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 41
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 28 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1998:167874 SCISEARCH
GA The Genuine Article (R) Number: YY117
TI The G-protein G(13) but not G(12) mediates signaling from lysophosphatidic acid receptor via **epidermal growth factor receptor** to Rho
AU Gohla A; Harhammer R; Schultz G (Reprint)
CS FREE UNIV BERLIN, INST PHARMAKOL, THIELALLEE 67-73, D-14195 BERLIN, GERMANY (Reprint); FREE UNIV BERLIN, INST PHARMAKOL, D-14195 BERLIN, GERMANY
CYA GERMANY
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (20 FEB 1998) Vol. 273, No. 8, pp. 4653-4659.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 35
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 29 OF 73 MEDLINE DUPLICATE 17
AN 1998187674 MEDLINE
DN 98187674
TI **Epidermal growth factor receptor** activation in androgen-independent but not androgen-stimulated growth of human prostatic carcinoma cells.
AU Sherwood E R; Van Dongen J L; Wood C G; Liao S; Kozlowski J M; Lee C
CS Department of Urology, Northwestern University Medical School, Chicago, IL 60611, USA.
NC DK 39250 (NIDDK)
CA 58073 (NCI)
SO BRITISH JOURNAL OF CANCER, (1998 Mar) 77 (6) 855-61.
Journal code: AV4. ISSN: 0007-0920.
CY SCOTLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199806

L12 ANSWER 30 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998174905 EMBASE
TI [Tyrosine kinase: Implications in tumorigenesis and new avenues for cancer treatment].

TYROSINE KINASE: IMPLICATIONS EN PATHOLOGIE TUMORALE ET PERSPECTIVES THERAPEUTIQUES.
AU Peyrade F.; Taillan B.; Lebrun C.; Baron V.; Dujardin P.
CS F. Peyrade, Svc. d'Hematologie-Medecine Interne, Hopital l'Archet I, BP 3079, 06202 Nice cedex 03, France
SO Revue de Medecine Interne, (1998) 19/5 (366-372).
Refs: 15
ISSN: 0248-8663 CODEN: RMEIDE
CY France
DT Journal; General Review
FS 006 Internal Medicine
016 Cancer
037 Drug Literature Index
LA French
SL English; French

L12 ANSWER 31 OF 73 MEDLINE DUPLICATE 18
AN 1998330492 MEDLINE
DN 98330492
TI **EGFR** blockade by tyrosine kinase inhibitor or monoclonal **antibody** inhibits growth, directs terminal differentiation and induces apoptosis in the human squamous cell carcinoma HN5.
AU Modjtahedi H; Affleck K; Stubberfield C; Dean C
CS The Institute of Cancer Research, McElwain Laboratories, Belmont, Sutton, Surrey, UK.
SO INTERNATIONAL JOURNAL OF ONCOLOGY, (1998 Aug) 13 (2) 335-42.
Journal code: CX5. ISSN: 1019-6439.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199810

L12 ANSWER 32 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 19
AN 1998:442844 BIOSIS
DN PREV199800442844
TI Anti-**EGFR** monoclonal **antibodies** which act as EGF, TGFalpha, HB-EGF and BTC antagonists block the binding of epiregulin to **EGFR**-expressing tumours.
AU Modjtahedi, Helmout (1); Komurasaki, Toshi; Toyoda, Hitoshi; Dean, Christopher
CS (1) Inst. Cancer Res., McElwain Lab., Belmont, Sutton, Surrey SM2 5NG UK
SO International Journal of Cancer, (Jan. 19, 1998) Vol. 75, No. 2, pp. 310-316.
ISSN: 0020-7136.
DT Article
LA English

L12 ANSWER 33 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1998:498091 SCISEARCH
GA The Genuine Article (R) Number: ZV933
TI Skin cancer chemopreventive effects of a flavonoid antioxidant silymarin are mediated via impairment of receptor tyrosine kinase signaling and perturbation in cell cycle progression
AU Ahmad N; Gali H; Javed S; Agarwal R (Reprint)
CS AMC CANC RES CTR, CTR CANC CAUSAT & PREVENT, 1600 PIERCE ST, DENVER, CO 80214 (Reprint); AMC CANC RES CTR, CTR CANC CAUSAT & PREVENT, DENVER, CO 80214; CASE WESTERN RESERVE UNIV, UNIV HOSP CLEVELAND, DEPT DERMATOL,
SKIN

DIS RES CTR, CLEVELAND, OH 44106; CASE WESTERN RESERVE UNIV, UNIV HOSP CLEVELAND, IRELAND CANC CTR, CLEVELAND, OH 44106
CYA USA
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (18 JUN 1998) Vol. 247, No. 2, pp. 294-301.
Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 0006-291X.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 51
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 34 OF 73 MEDLINE
AN 1998069862 MEDLINE
DN 98069862
TI Cell scattering and migration induced by autocrine transforming growth factor alpha in human glioma cells in vitro.
AU El-Obeid A; Bongcam-Rudloff E; Sorby M; Ostman A; Nister M; Westermark B
CS Department of Pathology, Uppsala University, University Hospital, Sweden.
SO CANCER RESEARCH, (1997 Dec 15) 57 (24) 5598-604.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199803

L12 ANSWER 35 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97036644 EMBASE
DN 1997036644
TI The enhanced tumorigenic activity of a mutant **epidermal growth factor receptor** common in human cancers is mediated by threshold levels of constitutive **tyrosine phosphorylation** and unattenuated signaling.
AU Huang H.-J.S.; Nagane M.; Klingbeil C.K.; Hong Lin; Nishikawa R.; Ji X.-D.; Huang C.-M.; Gill G.N.; Wiley H.S.; Cavenee W.K.
CS H.-J.S. Huang, Ludwig Institute for Cancer Research, 9500 Gilman Dr, San Diego, CA 92093-0660, United States. hhuang@ucsd.edu
SO Journal of Biological Chemistry, (1997) 272/5 (2927-2935).
Refs: 72
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
LA English
SL English

L12 ANSWER 36 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 97:906724 SCISEARCH
GA The Genuine Article (R) Number: YJ803
TI Epiregulin binds to **epidermal growth factor receptor** and ErbB-4 and induces **tyrosine phosphorylation** of **epidermal growth**

factor receptor, ErbB-2, ErbB-3 and ErbB-4
AU Komurasaki T (Reprint); Toyoda H; Uchida D; Morimoto S
CS TAISHO PHARMACEUT CO LTD, MED RES LABS, MOL BIOL LAB, 1-403 YOSHINO CHO, OHMIYASHI, SAITAMA 330, JAPAN (Reprint)
CYA JAPAN
SO ONCOGENE, (4 DEC 1997) Vol. 15, No. 23, pp. 2841-2848.
Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE, HAMPSHIRE, ENGLAND RG21 6XS.
ISSN: 0950-9232.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 49
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 37 OF 73 MEDLINE DUPLICATE 20
AN 1998054129 MEDLINE
DN 98054129
TI Reduced ability of transforming growth factor-alpha to induce EGF receptor
heterodimerization and downregulation suggests a mechanism of oncogenic synergy with ErbB2.
AU Gulliford T J; Huang G C; Ouyang X; Epstein R J
CS Division of Medicine, Imperial College School of Medicine, Charing Cross Hospital, London, UK.
NC R0169513
SO ONCOGENE, (1997 Oct) 15 (18) 2219-23.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199802

L12 ANSWER 38 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 97:193770 SCISEARCH
GA The Genuine Article (R) Number: WK897
TI Role of **epidermal growth factor receptor** and STAT-3 activation in autonomous proliferation of SUM-102PT human breast cancer cells
AU Sartor C I; Dziubinski M L; Yu C L; Jove R; Ethier S P (Reprint)
CS UNIV MICHIGAN, DEPT RADIAT ONCOL, DIV RADIAT & CANC BIOL, SCH MED, 1331 E ANN ST, ANN ARBOR, MI 48109 (Reprint); UNIV MICHIGAN, DEPT RADIAT ONCOL, DIV RADIAT & CANC BIOL, SCH MED, ANN ARBOR, MI 48109; H LEE MOFFITT CANC CTR, TAMPA, FL 33612
CYA USA
SO CANCER RESEARCH, (1 MAR 1997) Vol. 57, No. 5, pp. 978-987.
Publisher: AMER ASSOC CANCER RESEARCH, PUBLIC LEDGER BLDG, SUITE 816, 150 S. INDEPENDENCE MALL W., PHILADELPHIA, PA 19106.
ISSN: 0008-5472.
DT Article; Journal
FS LIFE; CLIN
LA English
REC Reference Count: 59
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 39 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 97:502806 SCISEARCH

GA The Genuine Article (R) Number: XG558
TI Receptor dimerization is not a factor in the signalling activity of a transforming variant **epidermal growth factor receptor** (EGFRvIII)
AU Chu C T; Everiss K D; Wikstrand C J; Batra S K; Kung H J; Bigner D D (Reprint)
CS DUKE UNIV, MED CTR, DEPT PATHOL, DURHAM, NC 27710 (Reprint); DUKE UNIV, MED CTR, DEPT PATHOL, DURHAM, NC 27710; DUKE UNIV, MED CTR, PREUSS LAB BRAIN TUMOR RES, DURHAM, NC 27710; CASE WESTERN RESERVE UNIV, DEPT MOL BIOL & MICROBIOL, CLEVELAND, OH 44106; UNIV NEBRASKA, MED CTR, DEPT BIOCHEM & MOL BIOL, OMAHA, NE 68198
CYA USA
SO BIOCHEMICAL JOURNAL, (15 JUN 1997) Vol. 324, Part 3, pp. 855-861.
Publisher: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON, ENGLAND W1N 3AJ.
ISSN: 0264-6021.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 44
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 40 OF 73 MEDLINE DUPLICATE 21
AN 1998012851 MEDLINE
DN 98012851
TI Modulation of the Kv1.3 potassium channel by receptor tyrosine kinases.
AU Bowlby M R; Fadool D A; Holmes T C; Levitan I B
CS Department of Biochemistry and Volen Center for Complex Systems, Brandeis University, Waltham, Massachusetts 02254, USA.
SO JOURNAL OF GENERAL PHYSIOLOGY, (1997 Nov) 110 (5) 601-10.
Journal code: I8N. ISSN: 0022-1295.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802

L12 ANSWER 41 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 97:870328 SCISEARCH
GA The Genuine Article (R) Number: YG489
TI Immunohistochemical assessment of proliferation markers and altered gene expression in archival specimens of ovarian epithelial tumors
AU Khalifa M A (Reprint); Lacher D A; Lage J M; Mannel R S; Walker J L; Angros L H; Min K W
CS MEM UNIV NEWFOUNDLAND, GEN HOSP, DEPT PATHOL, ST JOHNS, NF A1B 3V6, CANADA
(Reprint); MEM UNIV NEWFOUNDLAND, DEPT PATHOL, ST JOHNS, NF, CANADA
CYA CANADA
SO CANCER DETECTION AND PREVENTION, (NOV-DEC 1997) Vol. 21, No. 6, pp. 532-539.
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148.
ISSN: 0361-090X.
DT Article; Journal
FS CLIN
LA English
REC Reference Count: 45
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 42 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 22

AN 1997:261498 BIOSIS
DN PREV199799568101
TI Monoclonal **antibodies** directed against the EGF receptor show differential bindings of amphiregulin and EGF to the EGF receptor.
AU Modjtahedi, Helmout (1); Cohen, Bruce D.; Dean, Christopher
CS (1) Inst. Cancer Res., McElwain Lab., 15 Cotswold Road, Belmont, Sutton, Surrey SM2 5NG UK
SO International Journal of Oncology, (1997) Vol. 10, No. 2, pp. 339-347. ISSN: 1019-6439.
DT Article
LA English

L12 ANSWER 43 OF 73 MEDLINE DUPLICATE 23
AN 97346252 MEDLINE
DN 97346252
TI Protein kinase C inhibits **epidermal growth factor receptor** phosphorylation in enterocytes.
AU Summers S T; Bass B L
CS Department of Surgery, Veteran's Administration Medical Center, Baltimore, Maryland 21201, USA.
SO JOURNAL OF SURGICAL RESEARCH, (1997 Apr) 69 (1) 208-11. Journal code: K7B. ISSN: 0022-4804.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709

L12 ANSWER 44 OF 73 MEDLINE DUPLICATE 24
AN 97126968 MEDLINE
DN 97126968
TI Inhibition of **epidermal growth factor receptor**-associated tyrosine kinase blocks glioblastoma invasion of the brain.
AU Penar P L; Khoshyomn S; Bhushan A; Tritton T R
CS Division of Neurosurgery, University of Vermont College of Medicine, Burlington, USA.
SO NEUROSURGERY, (1997 Jan) 40 (1) 141-51. Journal code: NZL. ISSN: 0148-396X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705

L12 ANSWER 45 OF 73 CAPLUS COPYRIGHT 2001 ACS
AN 1996:71580 CAPLUS
DN 124:114575
TI Isolated polypeptide erbB-3, related to the **epidermal growth factor receptor** and **antibody** thereto
IN Kraus, Matthias H.; Aaronson, Stuart A.
PA United States Dept. of Health and Human Services, USA
SO U.S., 41 pp. Cont.-in-part of U.S. 5,183,884. CODEN: USXXAM
DT Patent
LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5480968	A	19960102	US 1992-978895	19921110
	US 444406	A0	19910315	US 1989-444406	19891201
	US 5183884	A	19930202		
	US 5820859	A	19981013	US 1995-473119	19950607
	US 5916755	A	19990629	US 1995-475352	19950607
PRAI	US 1989-444406	19891201			
	US 1992-978895	19921110			

L12 ANSWER 46 OF 73 MEDLINE DUPLICATE 25
AN 96215237 MEDLINE
DN 96215237
TI Involvement of ErbB2 in the signaling pathway leading to cell cycle progression from a truncated **epidermal growth factor receptor** lacking the C-terminal autophosphorylation sites.
AU Sasaoka T; Langlois W J; Bai F; Rose D W; Leitner J W; Decker S J; Saltiel A; Gill G N; Kobayashi M; Draznin B; Olefsky J M
CS First Department of Medicine, Toyama Medical and Pharmaceutical University, Toyama, 930-01, Japan.
NC DK33651 (NIDDK)
DK13149 (NIDDK)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Apr 5) 271 (14) 8338-44.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199608

L12 ANSWER 47 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 96:675245 SCISEARCH
GA The Genuine Article (R) Number: VG135
TI TARGETED INHIBITION OF TUMOR-CELL GROWTH BY A BISPECIFIC SINGLE-CHAIN TOXIN CONTAINING AN **ANTIBODY** DOMAIN AND TGF-ALPHA
AU SCHMIDT M; WELS W (Reprint)
CS INST EXPT CANC RES, TUMOR BIOL CTR, POB 1120, D-79011 FREIBURG, GERMANY (Reprint); INST EXPT CANC RES, TUMOR BIOL CTR, D-79011 FREIBURG, GERMANY; UNIV FREIBURG, DEPT BIOL, FREIBURG, GERMANY
CYA GERMANY
SO BRITISH JOURNAL OF CANCER, (SEP 1996) Vol. 74, No. 6, pp. 853-862.
ISSN: 0007-0920.
DT Article; Journal
FS LIFE; CLIN
LA ENGLISH
REC Reference Count: 28
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 48 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 96:99708 SCISEARCH
GA The Genuine Article (R) Number: TR538
TI BETACELLULIN ACTIVATES THE **EPIDERMAL GROWTH-FACTOR RECEPTOR** AND ERBB-4, AND INDUCES CELLULAR-RESPONSE PATTERNS DISTINCT FROM THOSE STIMULATED BY EPIDERMAL GROWTH-FACTOR OR NEUREGULIN-BETA

AU RIESE D J; BERMINGHAM Y; VANRAAIJ T M; BUCKLEY S; PLOWMAN G D; STERN D F (Reprint)
CS YALE UNIV, SCH MED, DEPT PATHOL, 333 CEDAR ST, NEW HAVEN, CT, 06520 (Reprint); YALE UNIV, SCH MED, DEPT PATHOL, NEW HAVEN, CT, 06520; BRISTOL MYERS SQUIBB PHARMACEUT RES INST, SEATTLE, WA, 98121; SUGEN INC, REDWOOD CITY, CA, 94063
CYA USA
SO ONCOGENE, (18 JAN 1996) Vol. 12, No. 2, pp. 345-353.
ISSN: 0950-9232.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 54
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 49 OF 73 MEDLINE DUPLICATE 26
AN 96313262 MEDLINE
DN 96313262
TI Intracellular expression of a single-chain **antibody** directed to the **EGFR** leads to growth inhibition of tumor cells.
AU Jannot C B; Beerli R R; Mason S; Gullick W J; Hynes N E
CS Friedrich Miescher Institute, Basel, Switzerland.
SO ONCOGENE, (1996 Jul 18) 13 (2) 275-82.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199611

L12 ANSWER 50 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 27
AN 1996:239871 BIOSIS
DN PREV199698788000
TI UV activates growth factor receptors via reactive oxygen intermediates.
AU Huang, Ruo-Pan; Wu, Jie-Xin; Fan, Yan; Adamson, Eileen D. (1)
CS (1) La Jolla Cancer Res. Foundation, 10901 N. Torrey Pines Rd., La Jolla, CA 92037 USA
SO Journal of Cell Biology, (1996) Vol. 133, No. 1, pp. 211-220.
ISSN: 0021-9525.
DT Article
LA English

L12 ANSWER 51 OF 73 MEDLINE DUPLICATE 28
AN 95197672 MEDLINE
DN 95197672
TI Association of **epidermal growth factor receptors** with coated pit adaptins via a **tyrosine phosphorylation**-regulated mechanism.
AU Nesterov A; Kurten R C; Gill G N
CS Department of Medicine, University of California at San Diego, La Jolla 92093.
NC PO1 CA58689 (NCI)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Mar 17) 270 (11) 6320-7.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals

EM 199506

L12 ANSWER 52 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 29
AN 1995:495418 BIOSIS
DN PREV199598518968
TI **Antibody**-induced inhibition of growth of **EGFR** overexpressing occurs in the absence of receptor down-regulation.
AU Modjtahedi, Helmout; Dean, Christopher
CS Inst. Cancer Res., Section Immunol., Sutton, Surrey SM2 5NG UK
SO International Journal of Oncology, (1995) Vol. 7, No. 4, pp. 783-788. ISSN: 1019-6439.
DT Article
LA English

L12 ANSWER 53 OF 73 MEDLINE
AN 95032035 MEDLINE
DN 95032035
TI Nuclear localization of p185neu tyrosine kinase and its association with transcriptional transactivation.
AU Xie Y; Hung M C
CS Department of Tumor Biology, University of Texas M. D. Anderson Cancer Center, Houston 77030.
NC CA58880 (NCI)
CA60856 (NCI)
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1994 Sep 30) 203 (3)
1589-98.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199501

L12 ANSWER 54 OF 73 CAPLUS COPYRIGHT 2001 ACS
AN 1994:401881 CAPLUS
DN 121:1881
TI Increased levels and constitutive **tyrosine phosphorylation** of the **epidermal growth factor receptor** contribute to autonomous growth of human papilloma virus type 16 immortalized human keratinocytes
AU Zyzak, Li Li; MacDonald, Lisa M.; Batova, Ayse; Forand, Ronald; Creek, Kim E.; Pirisi, Lucia
CS Sch. Med., Univ. South Carolina, Columbia, SC, 29208, USA
SO Cell Growth Differ. (1994), 5(5), 637-47
CODEN: CGDIE7; ISSN: 1044-9523
DT Journal
LA English

L12 ANSWER 55 OF 73 MEDLINE DUPLICATE 30
AN 94325221 MEDLINE
DN 94325221
TI Increased levels and constitutive **tyrosine phosphorylation** of the **epidermal growth factor receptor** contribute to autonomous growth of human papillomavirus type 16 immortalized human keratinocytes.
AU Zyzak L L; MacDonald L M; Batova A; Forand R; Creek K E; Pirisi L

CS Department of Pediatrics, University of South Carolina School of Medicine,
Columbia.
NC R29CA48990 (NCI)
SO CELL GROWTH AND DIFFERENTIATION, (1994 May) 5 (5) 537-47.
Journal code: AYH. ISSN: 1044-9523.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199411

L12 ANSWER 56 OF 73 CAPLUS COPYRIGHT 2001 ACS
AN 1994:209532 CAPLUS
DN 120:209532
TI Peptides that bind ligands of the **epidermal growth factor receptor** and erbB-2-receptor
IN Lupu, Ruth; Lippman, Marc
PA Georgetown University, USA
SO PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9322339	A1	19931111	WO 1993-US4055	19930429
	W: AU, CA, JP, NZ, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9342244	A1	19931129	AU 1993-42244	19930429
	AU 676476	B2	19970313		
	EP 641358	A1	19950308	EP 1993-910919	19930429
	EP 641358	B1	20000315		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 08502241	T2	19960312	JP 1993-519523	19930429
	AT 190626	E	20000415	AT 1993-910919	19930429
	US 5874528	A	19990223	US 1994-117187	19941027
PRAI	US 1992-875788	19920429			
	US 1992-917988	19920724			
	US 1990-528438	19900525			
	US 1991-640497	19910114			
	US 1992-872114	19920422			
	WO 1993-US4055	19930429			

L12 ANSWER 57 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 31
AN 93260696 EMBASE
DN 1993260696
TI eps15, A novel tyrosine kinase substrate, exhibits transforming activity.
AU Fazioli F.; Minichiello L.; Matoskova B.; Wong W.T.; Di Fiore P.P.
CS Lab. of Cellular/Molecular Biology, National Cancer Institute,Bethesda, MD
20892, United States
SO Molecular and Cellular Biology, (1993) 13/9 (5814-5828).
ISSN: 0270-7306 CODEN: MCEBD4
CY United States
DT Journal; Article

FS 029 Clinical Biochemistry
LA English
SL English

L12 ANSWER 58 OF 73 MEDLINE DUPLICATE 32
AN 93155115 MEDLINE
DN 93155115
TI Amphiregulin induces **tyrosine phosphorylation** of the **epidermal growth factor receptor** and p185erbB2. Evidence that amphiregulin acts exclusively through the **epidermal growth factor receptor** at the surface of human epithelial cells.
AU Johnson G R; Kannan B; Shoyab M; Stromberg K
CS Laboratory of Cell Biology, Food and Drug Administration, Bethesda, Maryland 20892.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Feb 5) 268 (4) 2924-31.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199305

L12 ANSWER 59 OF 73 MEDLINE
AN 93219392 MEDLINE
DN 93219392
TI Demonstration of ligand-dependent signaling by the erbB-3 tyrosine kinase and its constitutive activation in human breast tumor cells.
AU Kraus M H; Fedi P; Starks V; Muraro R; Aaronson S A
CS Laboratory of Cellular and Molecular Biology, National Cancer Institute, Bethesda, MD 20892.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1993 Apr 1) 90 (7) 2900-4.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199307

L12 ANSWER 60 OF 73 CAPLUS COPYRIGHT 2001 ACS
AN 1994:24253 CAPLUS
DN 120:24253
TI Down-modulation of **epidermal growth factor receptor** accompanies TNF-induced differentiation of the DiFi human adenocarcinoma cell line toward a goblet-like phenotype
AU Novotny-Smith, C. L.; Zorbas, M. A.; Mcisaac, A. M.; Irimura, T.; Boman, Bruce M.; Yeoman, L. C.; Gallick, G. E.
CS M. D. Anderson Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SO J. Cell. Physiol. (1993), 157(2), 253-62
CODEN: JCLLAX; ISSN: 0021-9541
DT Journal
LA English

L12 ANSWER 61 OF 73 MEDLINE DUPLICATE 33
AN 93179513 MEDLINE
DN 93179513
TI Anti-**epidermal growth factor**

receptor monoclonal **antibodies** affecting signal transduction.
AU Reins H A; Steinhilber G; Freiberg B; Anderer F A
CS Friedrich-Miescher-Laboratorium der Max-Planck-Gesellschaft, Tuebingen, Federal Republic of Germany.
SO JOURNAL OF CELLULAR BIOCHEMISTRY, (1993 Feb) 51 (2) 236-48. Journal code: HNF. ISSN: 0730-2312.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199306

L12 ANSWER 62 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 92:445454 SCISEARCH
GA The Genuine Article (R) Number: JF088
TI **TYROSINE PHOSPHORYLATION** OF MITOGEN-ACTIVATED PROTEIN-KINASE IN CELLS WITH TYROSINE KINASE-NEGATIVE **EPIDERMAL GROWTH-FACTOR RECEPTORS**
AU CAMPOSGONZALEZ R (Reprint); GLENNEY J R
CS UNIV KENTUCKY, LUCILLE P MARKEY CANC CTR, COMBS BLDG, RM 227, 800 ROSE ST, LEXINGTON, KY, 40536 (Reprint); UNIV KENTUCKY, DEPT BIOCHEM, LEXINGTON, KY, 40536
CYA USA
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (25 JUL 1992) Vol. 267, No. 21, pp. 14535-14538. ISSN: 0021-9258.
DT Note; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 23
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 63 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 92287258 EMBASE
DN 1992287258
TI Epidermal growth factor stimulates **tyrosine phosphorylation** in the neonatal mouse: Association of a M(r) 55,000 substrate with the receptor.
AU Donaldson R.W.; Cohen S.
CS Department of Biochemistry, Vanderbilt Univ. School of Medicine,Nashville, TN 37232, United States
SO Proceedings of the National Academy of Sciences of the United States of America, (1992) 89/18 (8477-8481). ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English

L12 ANSWER 64 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 34
AN 92:167053 SCISEARCH
GA The Genuine Article (R) Number: HH747
TI IDENTIFICATION AND BIOCHEMICAL-CHARACTERIZATION OF NOVEL PUTATIVE SUBSTRATES FOR THE **EPIDERMAL GROWTH-FACTOR**

RECEPTOR KINASE
AU FAZIOLI F; BOTTARO D P; MINICHIELLO L; AURICCHIO A; WONG W T; SEGATTO O; DIFIORE P P (Reprint)
CS NCI, CELLULAR & MOLEC BIOL LAB, BLDG 37, RM 1D23, BETHESDA, MD, 20892
CYA USA
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (15 MAR 1992) Vol. 267, No. 8, pp. 5155-5161.
ISSN: 0021-9258.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 46
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 65 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 92:120807 SCISEARCH
GA The Genuine Article (R) Number: HE606
TI P185C-NEU AND **EPIDERMAL GROWTH-FACTOR** **RECEPTOR** ASSOCIATE INTO A STRUCTURE COMPOSED OF ACTIVATED KINASES
AU QIAN X L; DECKER S J; GREENE M I (Reprint)
CS UNIV PENN, SCH MED, DEPT PATHOL & LAB MED, PHILADELPHIA, PA, 19104; UNIV PENN, SCH MED, DEPT BIOL, PHILADELPHIA, PA, 19104; PARKE DAVIS & CO, DIV PHARMACEUT RES, ANN ARBOR, MI, 48106
CYA USA
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (15 FEB 1992) Vol. 89, No. 4, pp. 1330-1334.
ISSN: 0027-8424.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 30
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 66 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 92:318395 SCISEARCH
GA The Genuine Article (R) Number: HU832
TI ANTIGEN RESPONSIVE **ANTIBODY**-RECEPTOR KINASE CHIMERA
AU UEDA H; KIKUCHI M; YAGI S; NISHIMURA H (Reprint)
CS UNIV TOKYO, FAC ENGN, DEPT CHEM ENGN, 7-3-1 HONGO, BUNKYO KU, TOKYO 113, JAPAN
CYA JAPAN
SO BIO-TECHNOLOGY, (APR 1992) Vol. 10, No. 4, pp. 430-433.
ISSN: 0733-222X.
DT Article; Journal
FS LIFE; AGRI
LA ENGLISH
REC Reference Count: 43
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 67 OF 73 CAPLUS COPYRIGHT 2001 ACS
AN 1992:52332 CAPLUS
DN 116:52332
TI Association of the tyrosine phosphorylated **epidermal growth factor receptor** with a 55-kD tyrosine phosphorylated protein at the cell surface and in endosomes
AU Wada, Ikuo; Lai, Wei H.; Posner, Barry I.; Bergeron, John J. M.
CS Dep. Anat., McGill Univ., Montreal, PQ, H3A 2B2, Can.
SO J. Cell Biol. (1992), 116(2), 321-30

CODEN: JCLBA3; ISSN: 0021-9525
DT Journal
LA English

L12 ANSWER 68 OF 73 MEDLINE DUPLICATE 35
AN 91271361 MEDLINE
DN 91271361
TI Phosphorylation of protein 4.1 on tyrosine-418 modulates its function in vitro.
AU Subrahmanyam G; Bertics P J; Anderson R A
CS Department of Pharmacology, University of Wisconsin Medical School, Madison 53706.
NC GM38906 (NIGMS)
CA47881 (NCI)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1991 Jun 15) 88 (12) 5222-6.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199109

L12 ANSWER 69 OF 73 MEDLINE
AN 92109790 MEDLINE
DN 92109790
TI Active c-erbB-2 induces short-term growth of FDC-P2 cells after IL-3 depletion.
AU Wongsasant B; Matsuda S; Yamamoto T
CS Department of Oncology, University of Tokyo, Japan.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1991 Dec 31) 181 (3)
981-8.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199204

L12 ANSWER 70 OF 73 MEDLINE
AN 92110038 MEDLINE
DN 92110038
TI Immunodetection of the ligand-activated receptor for epidermal growth factor.
AU Campos-Gonzalez R; Glenney J R Jr
CS Department of Biochemistry, University of Kentucky, Lexington 40536-0093.
NC GM-32866 (NIGMS)
SO GROWTH FACTORS, (1991) 4 (4) 305-16.
Journal code: AOI. ISSN: 0897-7194.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199204

L12 ANSWER 71 OF 73 MEDLINE DUPLICATE 36

AN 91019412 MEDLINE
DN 91019412
TI Direct interaction of a ligand for the erbB2 oncogene product with the EGF
receptor and p185erbB2.
AU Lupu R; Colomer R; Zugmaier G; Sarup J; Shepard M; Slamon D; Lippman M E
CS Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, DC 20007.
SO SCIENCE, (1990 Sep 28) 249 (4976) 1552-5.
Journal code: UJ7. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199101

L12 ANSWER 72 OF 73 MEDLINE DUPLICATE 37
AN 90338148 MEDLINE
DN 90338148
TI Cellular distribution and biological activity of **epidermal growth factor receptors** in A431 cells are influenced by cell-cell contact.
AU Lichtner R B; Schirrmacher V
CS Department of Immunology and Genetics, German Cancer Research Center, Heidelberg, Federal Republic of Germany.
SO JOURNAL OF CELLULAR PHYSIOLOGY, (1990 Aug) 144 (2) 303-12.
Journal code: HNB. ISSN: 0021-9541.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199011

L12 ANSWER 73 OF 73 MEDLINE DUPLICATE 38
AN 90147745 MEDLINE
DN 90147745
TI Expression of **epidermal growth factor receptor** sequences as E. coli fusion proteins: applications in the study of tyrosine kinase function.
AU Koland J G; O'Brien K M; Cerione R A
CS Department of Pharmacology, NYS College of Veterinary Medicine, Cornell University, Ithaca 14853.
NC GM40654 (NIGMS)
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1990 Jan 15) 166 (1)
90-100.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199005

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Association of the Tyrosine Phosphorylated Epidermal Growth Factor Receptor with a 55-kD Tyrosine Phosphorylated Protein at the Cell Surface and in Endosomes

Iku Wada, Wei H. Lai, Barry I. Posner,* and John J. M. Bergeron

Departments of Anatomy and Medicine,* McGill University, Montreal, Quebec, Canada H3A 2B2

Abstract. After the intraportal injection of EGF, the EGF receptor (EGFR) is rapidly internalized into hepatic endosomes where it remains largely receptor bound (Lai et al., 1989. *J. Cell Biol.* 109:2751–2760). In the present study, we evaluated the phosphotyrosine content of EGFRs at the cell surface and in endosomes in order to assess the consequences of internalization. Quantitative estimates of specific radioactivity of the EGFR in these two compartments revealed that tyrosine phosphorylation of the EGFR was observed at the cell surface within 30 s of ligand administration. However, the EGFR was also highly phosphorylated in endosomes reaching levels of tyrosine phosphorylation significantly higher than those of the cell surface receptor at 5 and 15 min after EGF injection. A 55-kD tyrosine phosphorylated polypeptide (pyp55) was observed in association with the EGFR at the cell surface within 30 s of EGF injection. The protein was also found in association with the EGFR in endosomes as evidenced by coprecipitation studies using a mAb to the EGFR as well as by coelution with the EGR in gel permeation chromatography. Limited proteolysis of isolated endosomes indicated that the tyrosine phosphorylated domains of the EGFR and associated pyp55 were cytosolically oriented while internalized EGF was intraluminal. The identification of pyp55 in association with EGFR in both hepatic plasma membranes and endosomes may be relevant to EGFR function and/or trafficking of the EGFR.

We and others have used subcellular fractionation and associated approaches in an attempt to delineate the components of rat liver involved in insulin, prolactin, and EGF receptor (EGFR)[1] internalization in vivo (Bergeron et al., 1985; Dunn and Hubbard, 1986; Khan et al., 1986, 1989; Lai et al., 1989*a*,*b*). Past studies have revealed that after internalization into endosomes (5–15 min) the ligand, EGF, remained largely associated with the periphery of endosomes. This was revealed by EM radioautography of the distribution of silver grains from [^{125}I]EGF within endosomes in situ of the placental syncytiotrophoblast (Lai et al., 1986) and for the distribution of [^{125}I]EGF within isolated rat liver endosomes (Lai et al., 1989*b*). Direct visualization of internalized EGF by protein-A gold EM immunolabeling of endosomes in A431 cells has been demonstrated by Carpentier et al. (1987) and biochemical studies that evaluated the degree of ligand receptor association after polyethylene glycol precipitation of the complexes from solubilized endosomes revealed that the majority of internalized EGF within such components of liver parenchymal cells was receptor bound (Lai et al., 1989*b*). These studies as well as the observations that demonstrated enhanced autophosphorylation activity of the EGFR in isolated rat liver endosomes (Kay et al., 1986; Lai et al., 1989*b*) predicted that the phosphotyrosine content of the EGFR subsequent to internalization must remain elevated at least during transit of the receptor through the endosomal compartment(s). We have attempted to test this prediction by quantitation of the in vivo state of tyrosine phosphorylation of the receptor at the cell surface and after internalization into endosomes. Larkin et al. (1986) demonstrated the feasibility of labeling hepatic receptors such as the polymeric IgA receptor after whole animal injection of ^{32}Pi. We have consequently followed this approach to label the EGFR in vivo, and in conjunction with antibodies specific to phosphotyrosine have observed that the EGFR is indeed highly tyrosine phosphorylated after internalization into endosomes after initial phosphorylation at the cell surface. Furthermore, we have observed a novel tyrosine phosphorylated protein of 55 kD (pyp55) in association with the EGFR both at the cell surface and after receptor internalization into endosomes. The orientation of the EGFR and pyp55 in isolated endosomes is such that their tyrosine phosphorylated domains are cytosolically oriented.

1. *Abbreviations used in this paper*: EGFR, EGF receptor; GE, Golgi endosomal; PM, plasma membrane.

Materials and Methods

Materials

EGF was purchased from Collaborative Research (Waltham, MA) and insulin was a gift from the Connaught Laboratories (Toronto, Ontario). [γ-^{32}P]-ATP (3,000 Ci/mmol), [^{32}P]orthophosphate (900 mCi/mmol), and Na[^{125}I]

were purchased from DuPont Canada (Mississauga, Ontario). Thin layer plates (E. Merck; 0.1 mm cellulose, 20 × 20 cm) were obtained from BDH (Montreal, Quebec). All other chemicals were from Sigma Chemical Co. (St. Louis, MO), Anachemia Canada Inc. (Lachine, Quebec), and Boehringer Mannheim (Montreal, Quebec). Sprague-Dawley rats were obtained from Charles River Ltd. (St. Constant, Quebec). For all experiments, rats were injected via the hepatic portal vein and sacrificed at various times after the injection of saturating doses (Lai et al., 1989*a*) of EGF (10 μg/100 g bw).

Antibodies

The hybridoma secreting anti-EGFR mAb was a gift from Dr. C. E. Chandler and was subcloned (IgG-151, BH-6) by Drs. W. A. Dunn and A. L. Hubbard (The Johns Hopkins University, Baltimore, MD). The antibodies were isolated from hybridomas as described by Lai et al. (1989*b*). Phosphotyrosine was conjugated to keyhole limpet hemocyanin by using 1-ethyl-3-(3-dimethyl amino)-1-naphthalene-sulfonic acid and was used to raise antibodies against phosphotyrosine in rabbits. Antibodies were obtained by phosphotyrosine conjugated to Affigel 15 (Bio Rad, Mississauga, Ontario) column chromatography. The specificity of the antibodies was evaluated by immunoprecipitation and immunoblotting of the tyrosine phosphorylated EGFR. Thus, both immunoprecipitation and Western blotting were inhibited by phosphotyrosine but not phosphoserine or phosphothreonine (not shown). Site-specific antibodies against peptide P1 (residues 1,164–1,176 KGSTRENAEYLRV) and against peptide P3 (DDTFLPVPEYINQS, residues 1,059–1,072) of the EGFR (Downward et al., 1984) were synthesized by Dr. N. Ling (The Salk Institute, San Diego, CA). The peptides were coupled to keyhold limpet hemocyanin and polyclonal antibodies were raised after injection into rabbits (Lai et al., 1989*a*).

In Vivo Labeling of Animals, Preparation of Plasma Membrane and Endosome Fractions, Determination of Receptor Content

Male Sprague-Dawley rats (120–130 g) received 5 mCi of [^{32}P]orthophosphate via the portal vein. EGF also was injected via the portal vein. The livers were removed at 1 h after the injection of [^{32}P] orthophosphate and homogenized immediately in ice-cold homogenization buffer (0.25 M sucrose, 1 mM $MgCl_2$, 5 mM iodoacetamide, 4 mM NaF, 100 μM Na_3VO_4, 10 mM β-glycerophosphate, 5 mM *p*-nitrophenylphosphate, 5 mM Na_2MoO_4, 0.5 mM ATP, 2 mM benzamidine, 500 KIU Aprotinin per ml, 0.5 mM PMSF, 20 mM Tris-HCl, pH 7.5) with the Dounce homogenizer (type B) to give a 15% (wt/vol) homogenate. The plasma membrane (PM) fraction was isolated from the homogenate basically as described by Kay et al. (1986) except for the addition of 0.5 mM ATP, 10 mM β-glycerophosphate, 5 mM *p*-nitrophenylphosphate (final concentrations) to the homogenate and all centrifugation buffers. The PM fraction was subsequently purified from the combined 280-*g* and 1,500-*g* pellets as described by Kay et al. (1986) and Lai et al. (1989*a*). The resultant supernatant was used to purify the endosome (GE) fractions. The supernatant was adjusted to 1.1 M sucrose by adding 2.3 M sucrose in homogenization buffer (vide supra). A discontinuous gradient of 0.4 and 0.95 M sucrose containing the same buffer constituents as above was overlaid above the load zone (1:1 vol). Subsequent centrifugation (85,000 g_{av} for 150 min, Beckman SW28 rotor without the brake) yielded a GE fraction at the interface of the 0.4 and 0.95 M sucrose layers. The fraction was identical to that described by Kay et al. (1986), Lai et al. (1989*a*,*b*) and Doherty et al. (1990) as evaluated by EM, SDS-PAGE, ligand binding ([^{125}I]EGF), and the enzyme activities of 5′ nucleotidase and galactosyl transferase (data not shown).

At 0, 0.5, 5, and 15 min after the portal vein injection of EGF (10 μg/100 g bw), PM and GE fractions were prepared and EGFR content was evaluated. However, the high concentration of internalized EGF in GE fractions prevented the determination of EGFR content from inhibition dose response binding data (Lai et al., 1989*a*). Consequently immunoblotting, using site-specific antibody directed against peptide P1 of the EGFR (vide supra, followed by densitometry as described by Lai et al. [1989*a*] [see Fig. 3 of this reference]) was used to determine a linear relationship between densitometry and receptor content over a range of 5–100 μg of subcellular fraction protein. The densitometric units derived from immunoblotting were normalized for the EGFR content of PM and GE fractions isolated from the livers of control (noninjected) rats as determined from [^{125}I]EGF inhibition dose response binding data.

Immunoprecipitation

PM or GE fractions were pelleted by centrifugation at 10,000 *g* for 20 min (PM) or 100,000 *g* for 45 min (GE) after a fourfold dilution with the homogenization buffer. To precipitate the EGFR, membranes were solubilized with 5% Triton X-100, 2.5% sodium deoxycholate, 10% glycerol, 0.15 M NaCl, 5 mM iodoacetamide, 5 mM *p*-nitrophenylphosphate, 2 mM Na_3VO_4, 20 mM NaF, 10 mM β-glycerophosphate, 50 mM sodium phosphate buffer, pH 7.5, at 4°C for 30 min and diluted 10-fold with 0.1% BSA, 0.15 M NaCl, 5 mM *p*-nitrophenylphosphate, 100 mM sodium phosphate buffer, pH 6, then centrifuged at 50,000 *g* for 30 min. mAb against the EGFR (100 μg protein, IgG) was added to the supernatant (from 1 mg protein of PM or GE) and incubated for 15 min at 0°C followed by another incubation with Pansorbin for 1 h at 4°C. The immune complex was washed five times (5 min, 10,000 *g*) with 0.1% BSA, 0.1% Triton X-100, 0.15 M NaCl, 2 mM Na_3VO_4, 10 mM β-glycerophosphate, 100 mM sodium phosphate buffer, pH 7.5. The immune complex was resuspended in 1.5% SDS, 5% glycerol, 50 mM Tris-HCl, pH 6.8, 5% β-mercaptoethanol, and incubated for 15 min at 65°C. SDS-PAGE was carried out with a gradient gel of 5–15% acrylamide. Resolved phosphoproteins on the gel were visualized by radioautography using Kodak X-OMAT X-ray films with enhancing screens. Intensity of the bands was quantified by densitometry with a Zeineh soft laser scanning densitometer interphased with an IBM PC using a GS350 Data System (Hoffer Scientific Instruments).

Gel Permeation Chromatography of Endosomal Proteins

The GE fraction was solubilized as described for immunoprecipitation (vide supra). The solubilized endosomes were filtered through a 0.22-μm filter and immediately applied onto a TSK 3000 SW column equilibrated with 0.15 M NaCl, 0.2% Tween 20, 10% glycerol, 0.1 mM sodium vanadate, 10 mM Tris-HCl, pH 7.5. The eluant (0.2 ml/min/tube) was fractionated by reversed phase HPLC and 1 ml of 80% ethanol/20% n-hexanes was added immediately into each fraction.

Peptide Mapping

Peptide mapping of [^{125}I]EGFR and [^{125}I]pyp55 was effected as follows: GE fractions isolated at 15 min after injection of EGF were solubilized with 1% Triton X-100, 0.5% deoxycholate, 10 mM Tris-HCl, pH 7.5, 10% glycerol for 15 min on ice and were incubated with ~10 U of alkaline phosphatase (purified from Bovine intestinal mucosa; Sigma Chemical Co., Type VII-N) for 10 min at room temperature. The sample was iodinated with 1 mCi of Na[^{125}I] by using Iodo Beads (Pierce). Free iodine was removed by Sephadex G-25 (10 × 50 mm) column chromatography equilibrated with 0.1% BSA, 0.1% Triton X-100, 10% glycerol, 0.15 M NaCl, 10 mM Tris-HCl, pH 7.5. The void fraction was centrifuged at 100,000 *g* for 30 min after preincubation with Pansorbin for 15 min at room temperature (in order to remove nonspecific binding to Pansorbin). The supernatant was then incubated with EGFR antibody for 15 min at room temperature followed by another incubation with Pansorbin for 10 min at room temperature. The immune complex was recovered by centrifugation (10,000 *g* for 5 min) and washed as described above. The immune complex was treated under nonreducing conditions in order to minimize contamination with IgG heavy chain with 1.5% SDS, 5% glycerol, 50 mM Tris-HCl, pH 6.8, at 65°C for 10 min and resolved by SDS-PAGE. The bands corresponding to the EGFR and pyp55 were excised and tryptic peptides were obtained as follows: gel pieces were washed with 85% acetone, 5% triethylamine, 5% acetic acid, 5% water, followed by 50 mM *N*-ethylmorpholine, then homogenized in 1 ml of 50 mM *N*-ethylmorpholine as described by Tornqvist et al. (1987). The gel suspensions were incubated with 50 μg of TPCK trypsin for 3 h at 37°C with rotation followed by incubation with another 50 μg/ml of TPCK trypsin for 10–12 h at 37°C as described by Tornqvist et al. (1987). [^{125}I] peptides were then resolved on cellulose plates at 500 V for 30 min in 30% formic acid for the 1st dimension, and the second dimension was chromatographed in *n*-butanol, acetic acid, pyridine, H_2O (6:12:40:48) as described in Fig. 4. The plates were exposed to X-ray film for 1 wk (EGFR) or 30 d (pyp55) after staining with ninhydrin.

Limited Protease Digestion of the EGFR in Endosomes

GE fractions were isolated 15 min after the injection of 10 μg/100 g bw of EGF as described (Lai et al., 1989*a*,*b*) in the presence of the phosphatase inhibitors, 2 mM NaF, 100 μM Na_3VO_4, and 5 mM *p*-nitrophenylphosphate. Fractions (25 μg membrane protein) were incubated with increasing concentrations of trypsin at 0°C for 30 min in the presence or absence of Triton X-100 following which aprotinin at 2.5 times the respective concentration of trypsin was added.

Results

Subcellular fractionation was employed to separate hepatic PM from endosome fractions of liver homogenates prepared at various times after the intraportal injection of saturating doses of EGF (10 μg/100 g bw; Lai et al., 1989*a*). This was followed by an assessment of EGF receptor concentration in the two fractions by quantitative immunoblotting with site-specific antibody to the EGFR as well as the level of tyrosine phosphorylation of the EGFR by in vivo labeling with ^{32}Pi.

Evaluation of Receptor Concentration in PM and Endosome Fractions

Rapid loss of receptor from the PM and rapid concentrative internalization into endosomes was observed (Table I *a* as described previously [Lai et al., 1989*a*]) with a 4.3-fold decrease in the concentration of EGFR in PM fractions and an 11-fold increase in receptor concentration in the endosome fraction during 15 min after the injection of EGF.

Phosphotyrosine Content of the EGFR

We next assessed the in vivo phosphorylation of the EGFR after sequential injections of ^{32}Pi and EGF after which specific immunoprecipitation of the EGFR was done on solubilized PM and endosome fractions isolated from the same liver homogenates (Table I *b*). After the injection of 5 mCi of ^{32}Pi, the specific radioactivity of hepatic ATP was evaluated by the method of England and Walsh (1976) and found to be constant at 0.74 Ci/mol for 30–75 min after injection. Consequently, 30 min after the injection of ^{32}Pi, EGF was injected and both PM and GE fractions were isolated from liver homogenates of rats killed at 0, 30 s, 5 and 15 min after injection. The EGFR was immunoprecipitated with mAb IgG 151-BH6 (Lai et al., 1989*b*) and subjected to SDS-PAGE. Maximum labeling of the receptor (170 kD) in the PM was observed at 30 s after the injection of EGF after which labeling diminished (Fig. 1 *A*). However, in endosomes, increased labeling was found up to 15 min after EGF injection. Alkali treatment of gels (Fig. 1 *B*) demonstrated labeling on phosphotyrosine residues for the immunoprecipitated EGFR in PM as well as in endosomes. Densitometry of the X-ray films of immunoprecipitated EGFR after SDS-PAGE and alkali treatment showed that alkali-resistant ^{32}P-label in EGFRs remained nearly constant in PM fractions (when expressed per mg cell fracti n protein), but increased markedly in endosomes (Table I *b*). This approach enabled an estimation of the specific radioactivity f the recept r (Table I *c*). Receptor-specific activity increased significantly in PM between 0 and 30 s after EGF injection but changed little thereafter. However, the specific radioactivity of the EGFR in the GE fracti n did not change for the first 30 s after ligand administration despite a twofold increase in receptor concentration (see Table I, *a* and *c*). Subsequently, receptor specific activity increased eightfold between 30 s and 5 min after ligand injection and remained constant to 15 min. Of note the specific radioactivity values of the EGFR in endosomes were 2.9- and 2.3-fold higher respectively than the corresponding values for the receptor in PM at 5 and 15 min after injection.

Qualitatively similar findings were observed when experiments were evaluated by immunoblotting with antiphosphotyrosine antibodies. Immunoblotting of total cell fraction protein transferred onto nitrocellulose sheets revealed a major immunoreactive polypeptide at 170 kD whose temporal immunoreactivity in PM and endosomes was similar to that of the ^{32}P-labeled immunoprecipitated EGFR (see Fig. 1). This was confirmed by immunoprecipitation studies which demonstrated that the major immunoreactive band at 170 kD was indeed the EGFR (Fig. 2 *B*).

Identification of an EGFR-associated Polypeptide of 55 kD

In the above experiments, a polypeptide of 55 kD was also immunoprecipitated by the EGFR antibody (Figs. 1 and 2). Because ^{32}P labeling of this protein persisted after alkali treatment of the gels and because it was detected by immunoblotting with phosphotyrosine antibody it is referred to as pyp55. Indeed, in both PM and endosome fractions the pyp55 band was the major antiphosphotyrosine reactive band besides that of the EGFR at 170 kD (Fig. 2). Other immunoreactive bands were observed at 47 and 64 kD (Fig. 2 *A*). However, these proteins did not coimmunoprecipitate consistently with the EGFR (see Figs. 1 and 2 *B*).

The immunoprecipitation studies (Figs. 1 and 2) suggested an association of pyp55 with the EGFR which was evaluated by an alternative approach (Fig. 3). Endosomal fractions,

Table I. Ligand-mediated Changes in the Content and Specific Radioactivity of the EGFR in PM and GE Fractions

	a Receptor content No. × 10^{-12}/mg protein‡		b ^{32}P phosphotyrosine units/mg protein§		c Specific radioactivity‖	
Time*	PM	GE	PM	GE	PM	GE
min						
0	1.59 ± 0.23	0.30 ± 0.1	3.2 ± 1.1	1.0 ± 0.6	2.0 ± 0.8	3.3 ± 2.5
0.5	1.02 ± 0.36	0.65 ± 0.16	10.0 ± 4.2	3.0 ± 1.0	10.2 ± 7.1	4.6 ± 2.0
5	0.52 ± 0.13	2.13 ± 0.39	6.6 ± 2.1	78.4 ± 16.5	12.6 ± 4.9	36.8 ± 10.7¶
15	0.37 ± 0.07	3.28 ± 0.26	6.2 ± 0.8	123.3 ± 10.3	16.7 ± 4.2	37.6 ± 4.4**

* Time (min) after the injection of EGF.
‡ Receptor content (mean [n = 4] ± SD) was calculated from quantitative immunoblotting as described in Materials and Methods.
§ ^{32}P-labeled EGFR was evaluated by densitometry of radioautographs of immunoprecipitated EGFR subjected by SDS-PAGE and alkali-treatment (mean [n = 3] ± SD).
‖ Specific radioactivity, calculated as the ratio of column b/column a.
¶ Significantly different from the specific radioactivity of the EGFR at 5 min in PM ($P < 0.05$; Student's *t* test).
** Significantly different from value in PM at 15 min ($P < 0.01$).

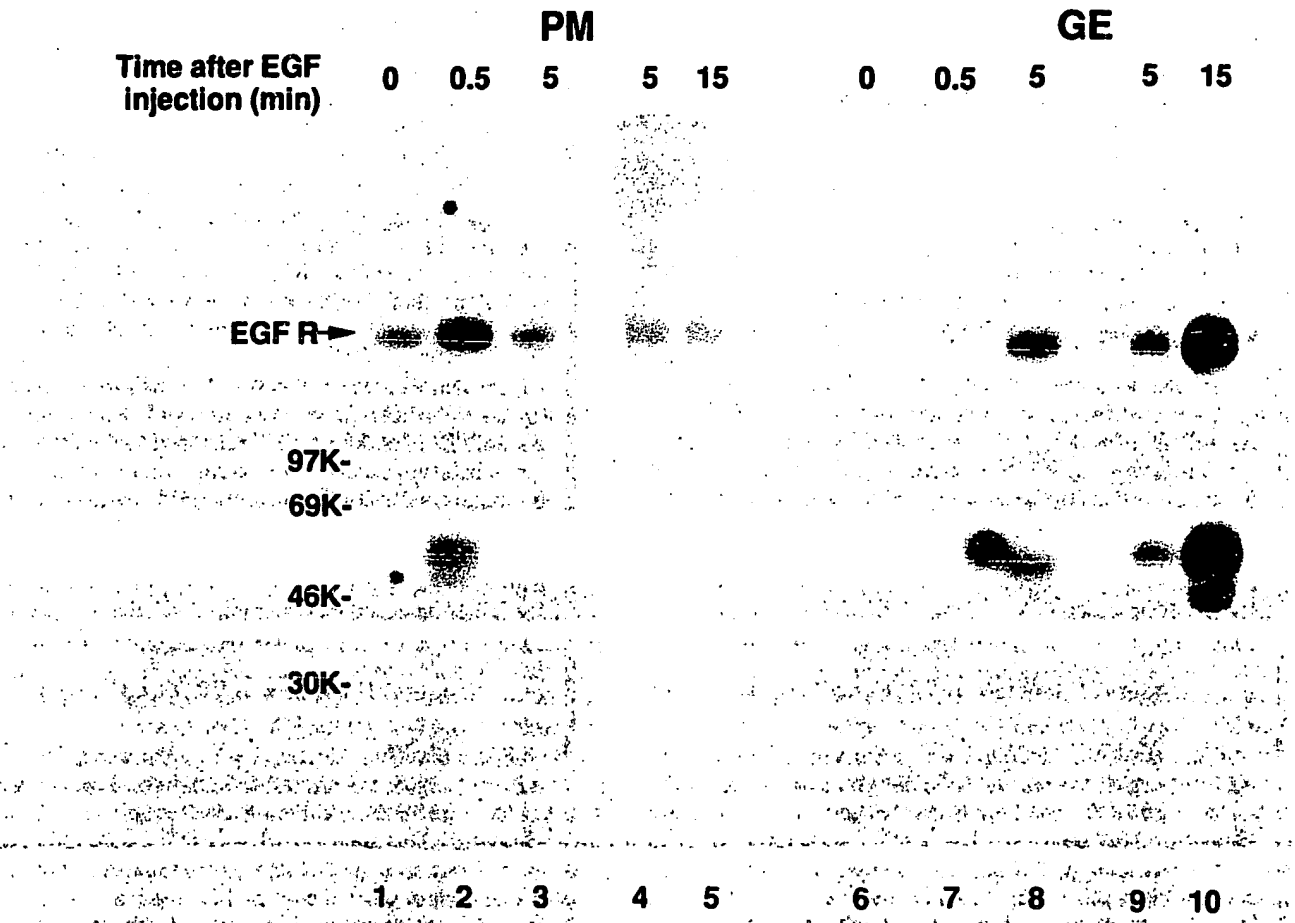

Figure 1. Immunoprecipitation of in vivo ^{32}P-labeled EGFR. (*A* and *B*) EGF was injected at 0, 30 s and 5 min (experiment I) or at 5 and 15 min (experiment II) into the portal vein of rats that had previously received 5 mCi of ^{32}P orthophosphate. PM and GE fractions were isolated and subjected to immunoprecipitation (PM, 700 μg; GE, 350 μg protein) followed by SDS-PAGE. All animals were killed at 60 min after injection of ^{32}P orthophosphate. The gels were exposed to X-ray film for 3 d (*A*; lanes *1–10*), then treated with alkali and re-exposed for 10 d (*B*). The position of the EGFR is indicated by the arrow. As well, in *B*, the mobilities of the phosphoprotein designated pyp55 and that of a band of molecular mass 47 kD (*asterisk*) are noted.

isolated 15 min after the injection of EGF, were solubilized and the proteins separated by HPLC gel permeation chromatography. Eluted fractions were electrophoresed, transferred to nitrocellulose sheets, and probed with the antiphosphotyrosine antibody as well as site-specific antibodies to the EGFR. Fractions eluting at a molecular weight of ~440,000 were reactive with both sets of antibodies. Two major proteins were immunoreactive with antiphosphotyrosine antibodies; one at a molecular mass of 170 kD corresponded to the EGFR as evidenced by immunoblotting with site specific antibodies. The other protein which was immunoreactive with antiphosphotyrosine antibody had a molecular mass identical to pyp55. Whereas the EGFR was found between fractions 8–15, pyp55 was restricted to fractions 8–11 as well as in monomeric form (~60,000 in molecular weight [not shown]). This was probably due to dissociation consequent to dilution during chromatography. However, the majority of the EGFR in endosomes was of higher order structure either in association with pyp55 (fractions 8–11) or with itself (fractions 12–15, ~340,000 in molecular weight).

Two-dimensional peptide analysis was carried out on the EGFR and pyp55 after solubilization, radiolabeling with Na[^{125}I], and immunoprecipitation with anti-EGFR antibody. No overlapping peptides were found (Fig. 4) indicating that pyp55 was a distinct protein. Attempts to generate phosphopeptide maps were unsuccessful due to the low level of ^{32}P incorporation and the lack of sensitivity of antiphosphotyrosine immunoblots after tryptic hydrolysis of the EGFR and pyp55 (data not shown and vide infra, Fig. 5).

Pyp55 did not bind to protein A (data not shown) and therefore was not related to the heavy chain of IgG (expected molecular mass ~55 kD). Furthermore, pyp55 was not immunologically related to *src* as mAb MA327 (Lipsich et al., 1983) to pp60^{src} (molecular mass 60 kD) did not immunoprecipitate pyp55 from solubilized endosomes. Neither was the protein related immunologically to the 55-kD tyrosine

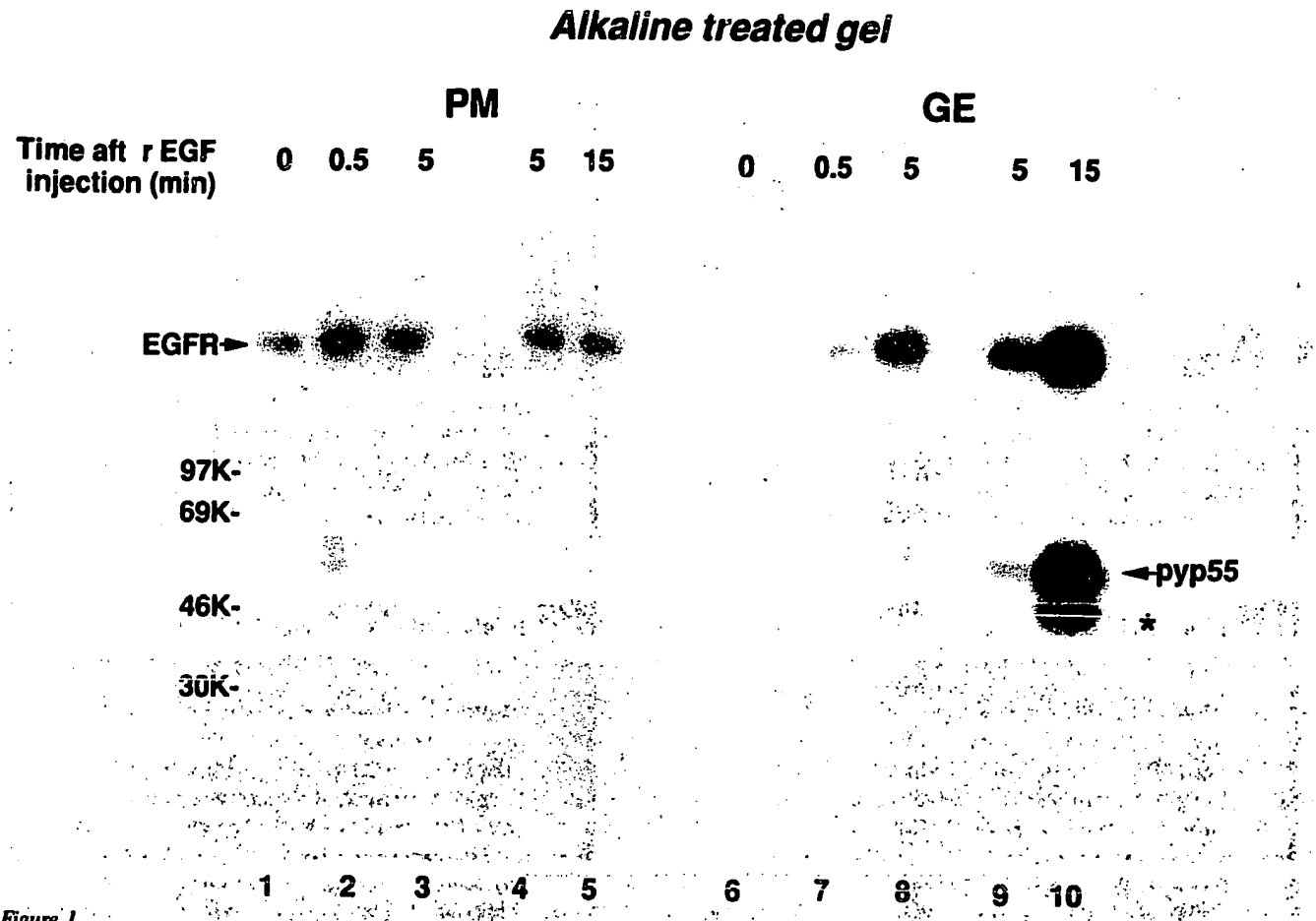

Figure 1.

phosphorylated protein identified by Baribault et al. (1989) since no reactivity was found on immunoblotting with antibodies to this protein with either immunoprecipitates of the EGFR or total endosomal proteins. Finally, phosphorylation of pyp55 was dependent on EGF. The administration of equivalent near saturating doses of insulin (15 μg/100 g bw) led to the endosomal accumulation of insulin receptors to levels similar to those of the EGFR shown in Table I. However, no association of pyp55 with the insulin receptor was found after immunoprecipitation nor was pyp55 phosphorylated after insulin administration as evaluated by Western blotting with antiphosphotyrosine antibody.

Orientation and Localization of the In Vivo Labeled EGFR in Endosomes

Isolated endosomes were subjected to limited proteolysis to evaluate the orientation of the EGFR and pyp55 in endosomes. Endosomes isolated 15 min after the injection of EGF were treated with increasing concentrations of trypsin at 0°C followed by immunoblotting with antiphosphotyrosine antibody. At the lowest dose of trypsin employed (0.4 μg/ml), immunoreactivity (with antiphosphotyrosine antibody) of the 170-kD EGFR as well as pyp55 was greatly diminished (Fig. 5 *A*; quantified in Fig. 5 *B*). Similar observati ns were found using site-specific antibody to the carboxyl-terminal tail of the EGFR (data not shown). By contrast, [^{125}I]EGF internalized into the same endosomes was insensitive to this limited protease digestion in the absence but not the presence of detergent (Fig. 5 *B*). Experiments were attempted to immunolocalize directly antiphosphotyrosine antibodies on isolated endosomes by the protein-A gold technique as described by Dominguez et al. (1991). These were, however, without success presumably due to the low signal (vide infra).

Discussion

Our studies and those of others (Dunn and Hubbard, 1986; Kay et al., 1986; Lai et al., 1989*a*) have demonstrated that after EGF administration, the EGFR is rapidly internalized into hepatic endosomes. We also found that the majority of endosomal ligand (EGF) remains receptor bound even 15 min after the injection of EGF (Lai et al., 1989*b*). The present study was undertaken to evaluate the phosphotyrosine content of the EGFR in isolated endosomes with comparison to what was observed at the cell surface.

The radioactivity in the ^{32}P-phosphotyrosine-labeled receptor was estimated by immunoprecipitating EGFR after the intraportal injection of ^{32}Pi. Accurate determination of EGFR concentration in the subcellular fracti ns was achieved by quantitative immunoblotting (see als Lai et al., 1989*a*)

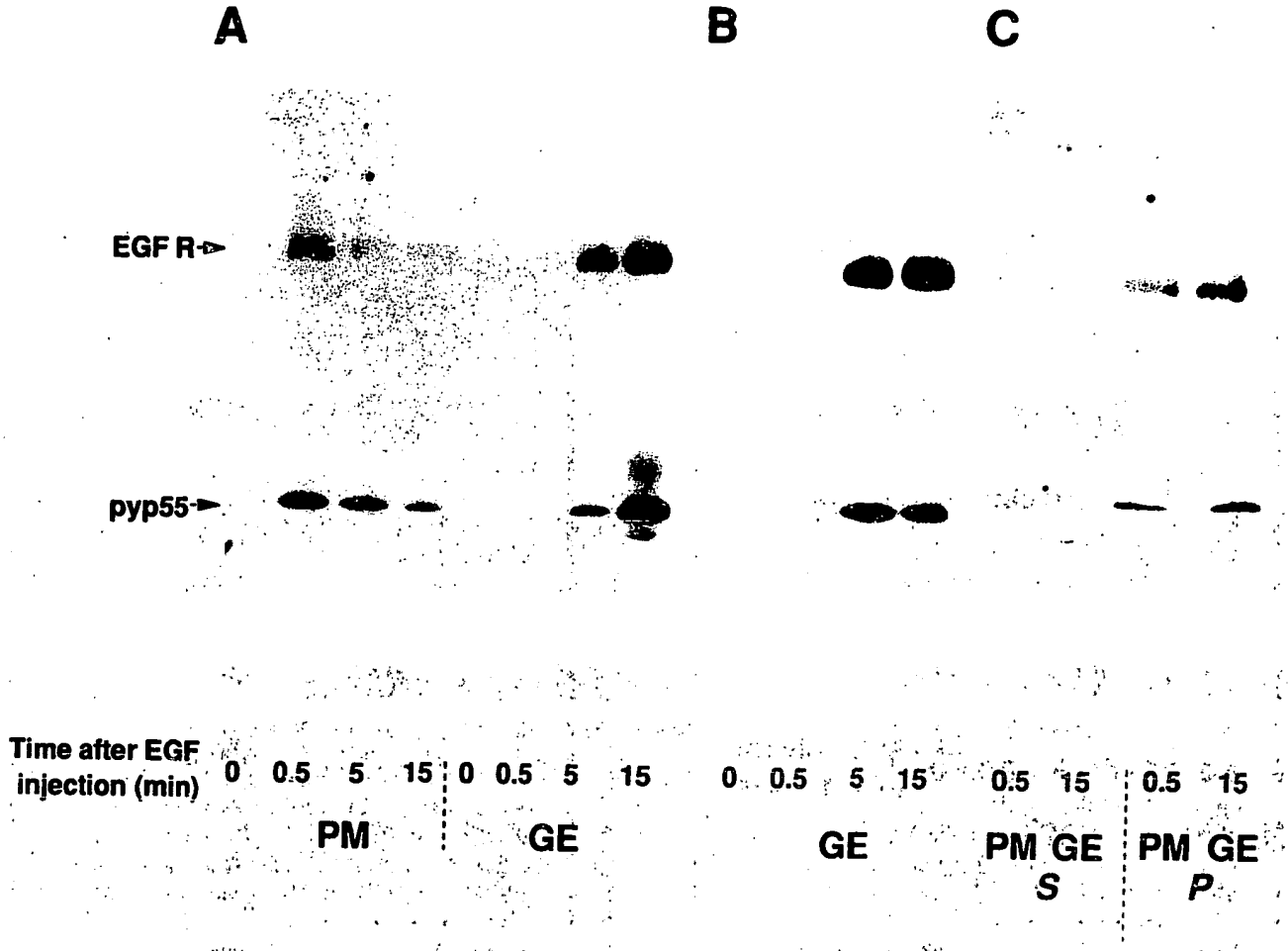

Figure 2. Immunoblot analysis of EGFR and substrates by anti-phosphotyrosine antibody. Membrane fractions (50 μg) of PM (lanes *1–4*) and GE (lanes *5–8*) were isolated from rats sacrificed at 0, 0.5, 5, and 15 min after the injection of EGF. (*A*) The fractions were subjected to SDS-PAGE and immunoblotted with antiphosphotyrosine antibody as described in Materials and Methods. (*B*) Endosomes (GE, 50 μg protein) were solubilized and after incubation with EGFR antibody, the immunoprecipitate was subjected to SDS-PAGE followed by immunoblotting with antiphosphotyrosine antibody. At 15 min after the injection of EGF additional bands at 47 and 64 kD are observed in addition to the EGFR and pyp55. (*C*) GE and PM fractions (100 μg protein each) isolated at 0.5 and 15 min after the injection of EGF were incubated with 0.1 M sodium carbonate on ice for 30 min followed by centrifugation at 200,000 *g* for 30 min. The supernatants (*S*) and pellets (*P*) were subjected to SDS-PAGE followed by immunoblotting with antiphosphotyrosine antibody. The positions corresponding to the molecular masses of the EGFR and pyp55 are indicated.

using a site-specific antibody to the EGFR. ^{32}P-phosphotyrosine content per unit receptor (i.e., specific radioactivity) was then calculated from the densitometry of ^{32}P-labeled immunoprecipitated EGFR divided by the receptor content. The data clearly establish that ligand-dependent tyrosine phosphorylation was initiated at the cell surface with a fivefold increase in receptor specific activity observed in plasma membranes within 30 sec after the administration of EGF. Endosomal receptor specific activity was significantly greater than that of PM receptors at either 5 ($P < 0.05$) or 15 min ($P < 0.01$) after injection. However, when calculated as the fold increase in specific activity over that at zero time, receptor-specific activity in endosomes at 15 min was only slightly greater (11.4-fold increase) than that calculated for PM over the same time interval (8.4-fold increase). (This discrepancy was due to the high variation in the estimation of the low receptor concentration and low ^{32}P-labeling of the EGFR in the GE fraction at zero time (Table I *c*)). Though consistent with the view that receptor phosphorylation was enhanced in endosomes our data do not exclude the possibility that receptor phosphorylation occurred only in the PM with highly phosphorylated receptors being preferentially internalized. On the other hand, within the first 30 s after EGF injection PM receptor specific activity increased fivefold whereas endosomal receptor specific activity remained similar to the low zero time level despite a twofold increase in receptor concentration in endosomes. Here there would appear to have been selective internalization of only poorly phosphorylated cell surface EGFRs. Thus the hypothesis of selective internalization appears to be a rather more complicated explanation for our data.

The yield of the PM fraction was ~14% based on the

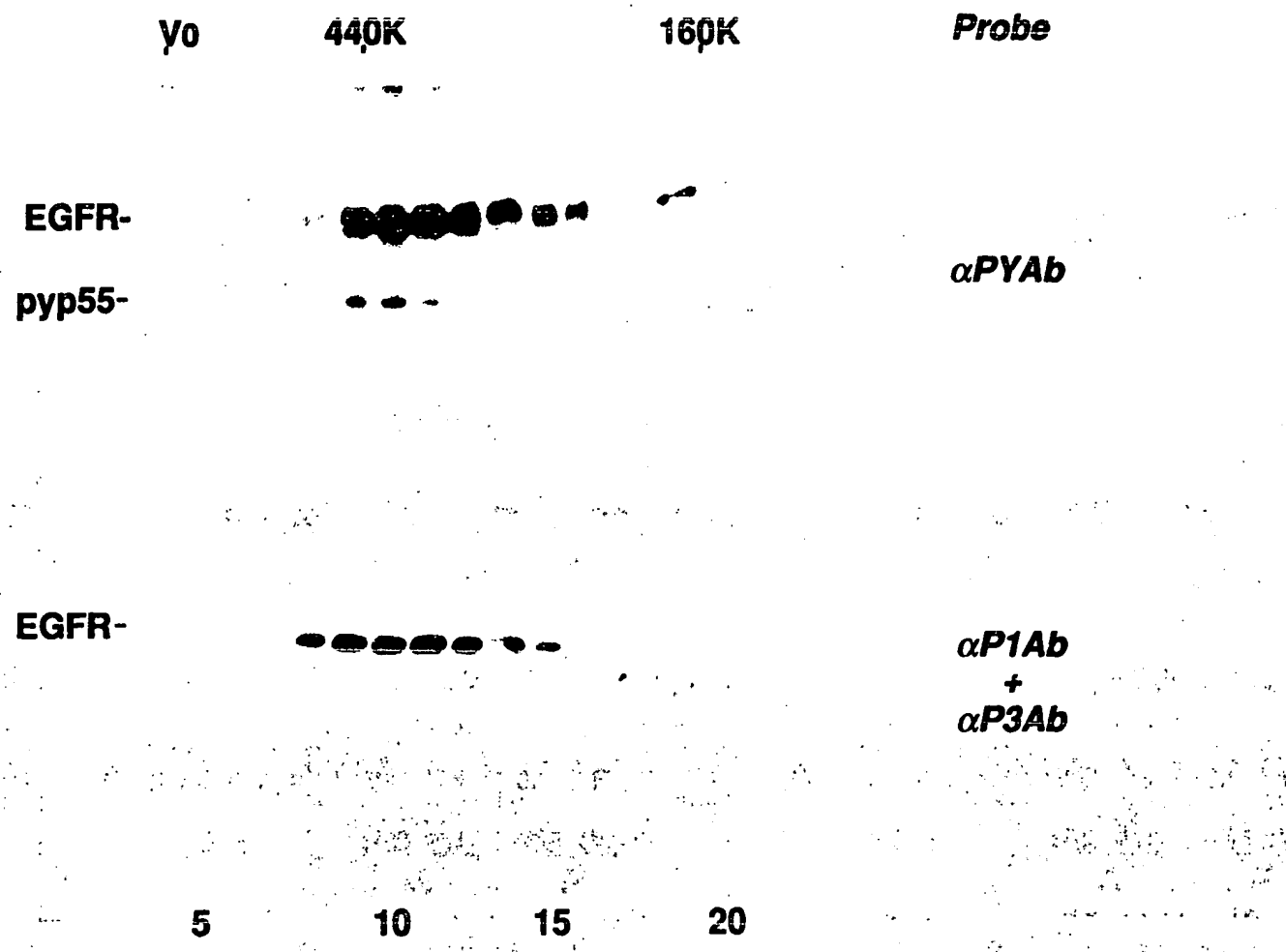

Figure 3. Coelution of pyp55 with EGFR in gel permeation chromatography. GE fractions (250 μg protein) isolated 15 min after the injection of EGF (10 μg/100 g bw) were solubilized as described in Materials and Methods. Eluted fractions were subjected to immunoblotting with the anti-phosphotyrosine antibody (*upper panel*) or a mixture of site-specific antibodies against synthetic peptides corresponding to residues 1,164–1,176 (αP1 Ab) and 1,059–1,072 (αP3 Ab) of the EGFR. Vo, void volume; 440 K, elution position of ferritin; 160 K, elution position of γ-globulin. On the left is indicated the positions of the EGFR and pyp55.

receptor content of these fractions compared to that of a total particulate fraction (Lai et al., 1989*a*). The yield of endosomes was ~32% (calculated from the receptor content in endosomes at 15 min after injection of saturating levels of EGF (Table I of the present study and Lai et al., 1989*a*) as compared to that of total particulate fractions of liver homogenates (Lai et al., 1989*a*). EM of the PM fraction indicated a representative cell fraction consisting of all domains (sinusoidal, lateral, bile canalicular) of the hepatic cell surface (Hubbard et al., 1983; Lai et al., 1989*a*). This was not the case for the endosomal fraction. The endosomal components of the GE fraction consisted mainly of tubulovesicular profiles with the vesicular components of ~250–300 nm in diameter containing intraluminal lipoprotein-like particles (Lai et al., 1989*b*; D herty et al., 1990). The much larger (and denser) multivesicular bodies were not found in this fraction. Indeed, the studies employing limited proteolysis of the GE fraction (Fig. 5) demonstrated that the tyrosine phosphorylated domain of the EGFR was cytosolically oriented while internalized [^{125}I]EGF was intraluminal. Taken together with past studies showing that at this dose of injected ligand and at 15 min after injection, [^{125}I]EGF was largely receptor bound and localized to the bounding membrane of endosomes (Lai et al., 1989*b*); we conclude that little if any of internalized EGF or tyrosine-phosphorylated EGFR was sequestered within intraluminal vesicles of multivesicular bodies in the GE fraction. Other investigators have clearly demonstrated internalized EGFR within such structures (McKanna et al., 1979; Hopkins, 1990; McCune et al., 1990). It is, however, noteworthy that Carpentier et

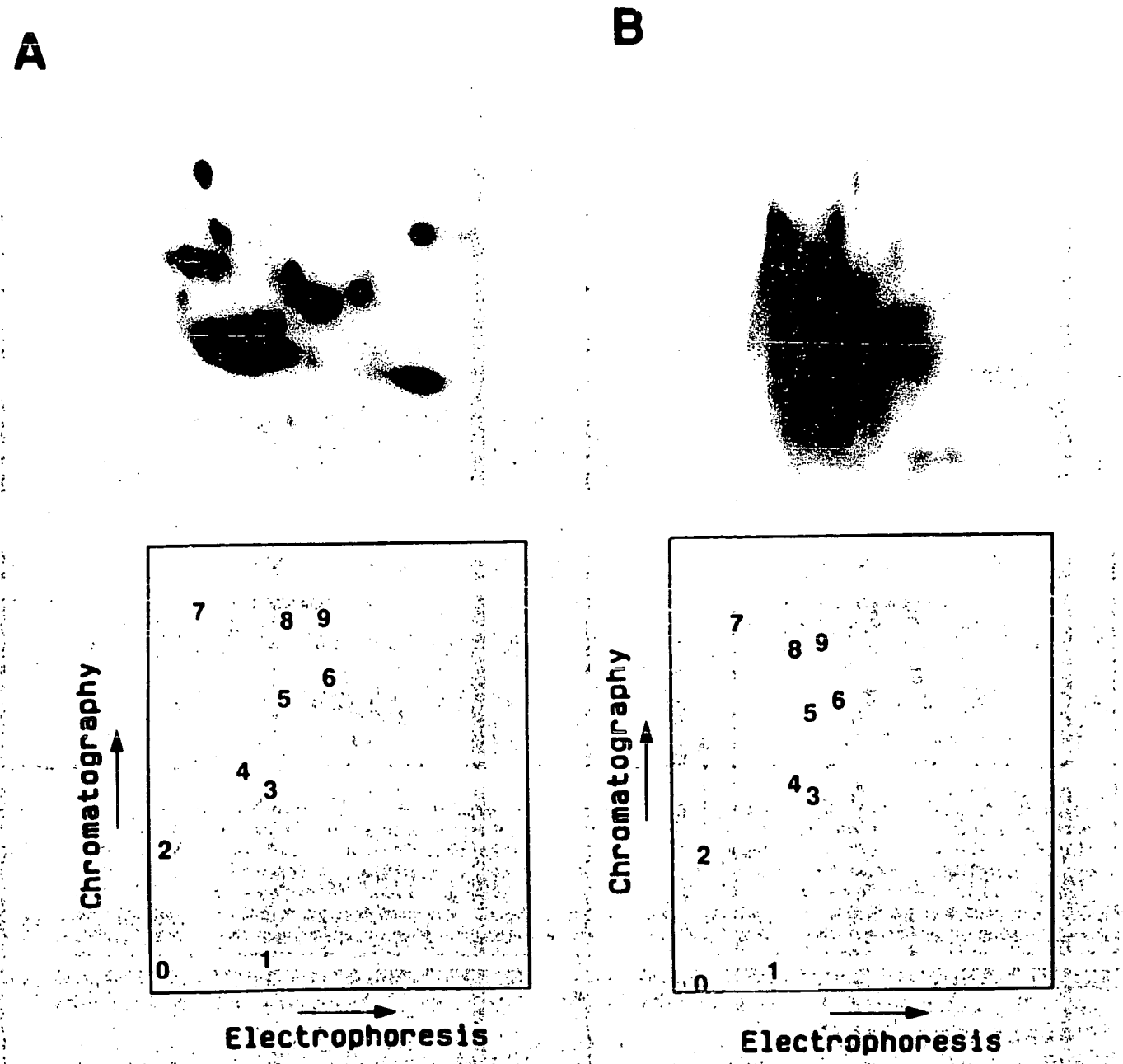

Figure 4. Two dimensional peptide maps of EGFR (*A*) and pyp55 (*B*). GE fractions were isolated at 15 min after the injection of EGF. The fractions were solubilized, dephosphorylated, and iodinated with Na[^{125}I] as described in Materials and Methods. After immunoprecipitation with mAb.to the EGFR, the radioiodinated EGFR and pyp55 were resolved by nonreducing SDS-PAGE, extracted from the gel, and digested with TPCK trypsin. Resulting peptides were applied onto a cellulose plate equilibrated with 30% formic acid and the [^{125}I] labeled tryptic peptides were resolved electrophoretically in 30% formic acid, then by chromatography in *n*-butanol/acetic acid/pyridine/H_2O (60:12:40:48). The plates were stained with ninhydrin and were exposed to X-ray film. In each case, the origin is indicated (o). None of the major [^{125}I] peptides of the EGFR (*A*) corresponded to those of pyp55 (*B*). The numbers indicate the locations of the ninhydrin positive spots which were due to degraded fragments of trypsin and used to align the two maps.

al. (1987) have immunolocalized phosphotyrosine to the cytosolic surface of endosomes in A431 cells after the administration of EGF. Even so, A431 cells have been reported by Wiley et al. (1988) to be defective in internalization of the EGFR. Hence, the studies of Carpentier et al. (1987) may have underestimated the significance of phosphotyrosine labeling in endosomes. A431 cells have been reported to have ca. 2×10^6 receptors per cell (Haigler et al., 1979; Krupp et al., 1982; Gamou et al., 1984). The much larger hepatocyte has less than 10^5 receptors per cell (Lai et al., 1989*a*). It was perhaps not surprising therefore that our own attempts to visualize phosphotyrosine labeling in endosomes by EM immunolabeling were unsuccessful (not shown).

In vivo labeling of the EGFR was determined after immu-

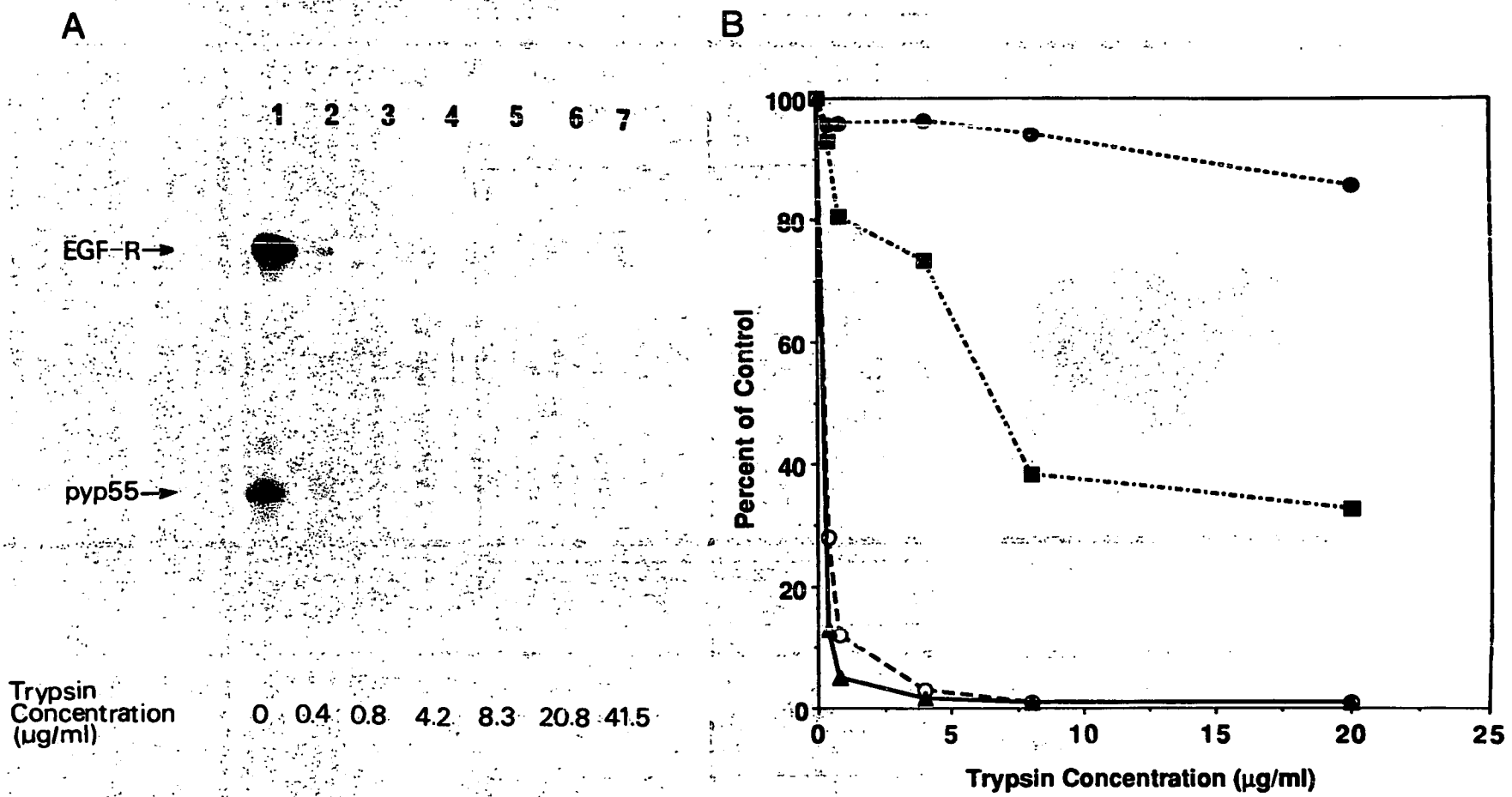

Figure 5. Orientation and localization in intact endosomes of the in vivo phosphorylated EGFR and pyp55. GE fractions were isolated 15 min after the injection of unlabeled EGF (10 μg/100 g bw). The fractions (15 μg membrane protein) were incubated with increasing concentrations of trypsin as described in Materials and Methods, then electrophoresed by SDS-PAGE, the proteins transferred to nitrocellulose sheets and probed with antiphosphotyrosine antibodies (*A*). The proportion of phosphotyrosine reactive EGFR (170 kD) (○ ···○) and pyp55 (55 kD) (▲—▲) were then estimated by densitometry (*B*). The proportion of protease sensitive internalized [^{125}I]EGF in endosomes was determined on concurrent experiments carried out in the presence (■—■) or absence (● ···●) of Triton X-100.

noprecipitati n with a mAb to the EGFR. Coprecipitating with the EGFR was an associated phosphotyrosine-labeled protein (pyp55) whose tyrosine phosphorylation was EGF dependent. Pyp55 was also readily seen n immunoblotting PM and ndosome fractions with antiphosphotyrosine antibodies. It was concluded that the protein was specifically associated with the EGFR in endosomes on the basis of its coprecipitation as well as by its demonstrated association during HPLC gel permeation chromatography of solubilized endosomes. The molecular weight of the EGFR:pyp55 complex was estimated by gel permeation chromatography to be ~440,000 which would be consistent with 2 mol of the EGFR and 2 mol of pyp55. The phosphoprotein pyp55 was found in association with the EGFR at initial times of activation at the cell surface, i.e., at 30 s as well as at peak times of internalization in endosomes (5–15 min). It was not possible to identify by Coomassie blue staining the amount of this protein in immunoprecipitates since it was below the limit of detection.

From their studies on the regulation of recycling of the Fc receptor, Mellman et al. (1984) have proposed that conditions favoring Fc receptor oligomerization would lead to downregulation while conditions favoring receptor monomer formation would lead to receptor recycling. The studies of Honegger et al. (1987) and Felder et al. (1990) have suggested that the tyrosine kinase activity of the EGFR in endosomes may be necessary for downregulation. Since our experimental conditions (EGF dose of 10 μg/100 g bw) favored downregulation (Lai et al., 1989*a*) we suggest that a possible function of pyp55 is to regulate the oligomerization of the EGFR in endosomes in a tyrosine phosphorylation dependent manner thereby regulating receptor downregulation. Current experiments aimed at purifying pyp55 and determining its primary structure by cDNA cloning could help elucidate the significance of this EGFR-associated phosphoprotein.

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References

Baribault, H., R. Blouin, L. Bourgon, and N. Marceau. 1989. Epidermal growth factor-induced selective phosphorylation of cultured rat hepatocyte 55-kD cytokeratin before filament reorganization and DNA synthesis. *J. Cell Biol.* 109:1665–1676.

Bergeron, J. J. M., J. Cruz, M. N. Khan, and B. I. Posner. 1985. Uptake of insulin and other ligands into receptor rich endocytic components of target cells: the endosomal apparatus. *Annu. Rev. Physiol.* 47:383–403.

Carpentier, J.-L., M. F. White, L. Orci, and R. C. Kahn. 1987. Direct visualization of the phosphorylated epidermal growth factor receptor during its internalization in A-431 cells. *J. Cell Biol.* 105:2751–2762.

Doherty, II, J.-J., D. G. Kay, W. H. Lai, B. I. Posner, and J. J. M. Bergeron. 1990. Selective degradation of insulin within rat liver endosomes. *J. Cell Biol.* 110:35–42.

Dominguez, J. M., J. Lanoix, J. Paiement. 1991. Localization of ras antigenicity in rat hepatocyte plasma membrane and rough endoplasmic reticulum fractions. *Exp. Cell Res.* 192:137–147.

Downward, J., P. Parker, and M. D. Waterfield. 1984. Autophosphorylation sites on the epidermal growth factor receptor. *Nature (Lond.).* 311:483–485.

Dunn, W. A., and A. L. Hubbard. 1986. Receptor-mediated endocytosis of epidermal growth factor by rat hepatocytes: receptor pathway. *J. Cell Biol.* 102:24–36.

England, P. J., and D. A. Walsh. 1976. A rapid method for the measurement of [γ-^{32}P]ATP specific radioactivity in tissue extracts and its application to the study of ^{32}Pi uptake in perfused rat heart. *Anal. Biochem.* 75:429–435.

Felder, S., K. Miller, G. Moehren, A. Ullrich, J. Schlessinger, and C. R. Hopkins. 1990. Kinase activity controls the sorting of EGF receptor within the multivesicular endosome. *Cell.* 61:623–634.

Gamou, S., Y. S. Kim, and N. Shimizu. 1984. Different responses to EGF in two human carcinoma cell lines, A431, and UCVA-1; possessing high numbers of EGF receptors: *Mol. Cell Endocrinol.* 3:205–213.

Haigler, H. T., J. A. McKanna, and S. Cohen. 1979. Direct visualization of a ferritin conjugate of epidermal growth factor in human carcinoma cells A-431. *J. Cell Biol.* 81:382–395.

Honegger, A. M., T. J. Dull, S. Felder, E. Van Obberghem, F. Bellot, D. Szapary, A. Schmidt, A. Ullrich, and J. Schlessinger. 1987. Point mutation at the ATP binding sites of EGF receptor abolishes protein-tyrosine kinase activity and alters cellular routing. *Cell.* 51:199–209.

Hopkins, C. R., A. Gibson, M. Shipman, and K. Miller. 1990. Movement of internalized ligand-receptor complexes along a continuous endosomal reticulum. *Nature (Lond.).* 346:335–339.

Hubbard, A. L., D. A. Wall, and A. Ma. 1983. Isolation of rat hepatocyte plasma membranes. I. Presence of the three major domains. *J. Cell Biol.* 96: 217–229.

Kay, D. G., W. H. Lai, M. Uchihashi, M. N. Khan, B. I. Posner, and J. J. M. Bergeron. 1986. Epidermal growth factor receptor kinase translocation and activation in vivo. *J. Biol. Chem.* 261:8473–8480.

Khan, M. N., S. Savoie, J. J. M. Bergeron, and B. I. Posner. 1986. Characterization of rat liver endosomal fractions: in vivo activation of insulin stimulable receptor kinase in these structures. *J. Biol. Chem.* 261:8462–8472.

Khan, M. N., G. Baquiran, C. Brule, J. Burgess, B. Foster, J. J. M. Bergeron, and B. I. Posner. 1989. Internalization and activation of the rat liver insulin receptor kinase in vivo. *J. Biol. Chem.* 264:12931–12940.

Krupp, M. N., D. T. Connolly, and M. D. Lane. 1982. Synthesis, turnover and down-regulation of epidermal growth factor receptors in human A-431 epidermoid carcinoma cells and skin fibroblasts. *J. Biol. Chem.* 257:11489–11496.

Lai, W. H., H. J. Guyda, and J. J. M. Bergeron. 1986. Binding and internalization of epidermal growth factor in human term placental cells in culture. *Endocrinology.* 118:413–423.

Lai, W. H., P. H. Cameron, I. Wada, J.-J. Doherty II, D. G. Kay, B. I. Posner, and J. J. M. Bergeron. 1989*a*. Ligand-mediated internalization, recycling, and down-regulation of the epidermal growth factor receptor in vivo. *J. Cell Biol.* 109:2741–2749.

Lai, W. H., P. H. Cameron, J.-J. Doherty, II, B. I. Posner, and J. J. M. Bergeron. 1989*b*. Ligand-mediated autophosphorylation activity of the epidermal growth factor receptor during internalization. *J. Cell Biol.* 109:2751–2760.

Larkin, J. M., E. S. Sztul, and G. E. Palade. 1986. Phosphorylation of the rat hepatic polymeric IgA receptor. *Proc. Natl. Acad. Sci. USA.* 83:4759–4763.

Lipsich, L. A., A. J. Lewis, J. S. Brugge. 1983. Isolation of monoclonal antibodies that recognize the transforming proteins of avian sarcoma viruses. *J. Virol.* 48:352–360.

McCune, B. K., C. A. Prokop, and H. S. Shelton. (1990). Transient epidermal growth factor (EGF)-dependent suppression of EGF receptor autophosphorylation during internalization. *J. Biol. Chem.* 265:9715–9721.

McKanna, J. A., H. T. Haigler, and S. Cohen. 1979. Hormone receptor topology and dynamics: morphological analysis using ferritin-labeled epidermal growth factor. *Proc. Natl. Acad. Sci. USA.* 76:5689–5693.

Mellman, I., H. Plutner, and P. Ukkonen. 1984. Internalization and rapid recycling of macrophage Fc receptors tagged with monovalent antireceptor antibody: possible role of a prelysosomal compartment. *J. Cell Biol.* 98:1163–1169.

Tornqvist, H. E., M. W. Pierce, A. R. Frackelton, R. A. Nemenoff. 1987. Identification of insulin receptor tyrosine residues autophosphorylated in vitro. *J. Cell Biol.* 262:10212–10219.

Wiley, H. S. 1988. Anomalous binding of epidermal growth factor to A-431 cells is due to the effect of high receptor densities and a saturable endocytic system. *J. Cell Biol.* 107:801–810.